

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number  
**WO 2004/045509 A2**

- (51) International Patent Classification<sup>7</sup>: **A61K**
- (21) International Application Number:  
PCT/US2003/035739
- (22) International Filing Date:  
11 November 2003 (11.11.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/427,198 18 November 2002 (18.11.2002) US
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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/045509 A2

(54) Title: METHOD OF USING A COX-2 INHIBITOR AND A 5-HT<sub>1A</sub> RECEPTOR MODULATOR AS A COMBINATION THERAPY

(57) Abstract: Compositions and methods to treat or prevent pain, inflammation, or inflammation-related disorder, as well as a neurologic disorder involving neurodegeneration in a subject that is in need of such prevention or treatment involve a combination of a Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator.

**METHOD OF USING A COX-2 INHIBITOR AND A 5-HT<sub>1A</sub>  
RECEPTOR MODULATOR AS A COMBINATION THERAPY  
CROSS-REFERENCE TO RELATED PATENTS AND PATENT  
APPLICATIONS**

5     **[0001]**     This application is a non-provisional of United States  
Provisional Patent Application No. 60/427,198, filed November 18, 2002,  
which is incorporated herein by reference in its entirety.

**BACKGROUND OF THE INVENTION**

(1) Field of the invention:

10    **[0002]**     The present invention relates to compositions and methods for  
the treatment or prevention of pain, inflammation, or inflammation-related  
disorder in a mammal using a combination of a Cox-2 inhibitor and a 5-  
HT<sub>1A</sub> receptor modulator.

(2) Description of related art:

15    **[0003]**     Serotonin (5-hydroxytryptamine, or 5-HT) is involved in the  
origin of many disease states. Recently, at least fourteen different 5-HT  
receptor subtypes have been identified and characterized ("A Review of  
Central 5-HT Receptors and Their Function," N. M. Barnes and T. Sharp,  
*Neuropharmacology*, 38:1083-1152 (1999)). The 5-HT<sub>1</sub> receptor family  
20    consists of five receptor subtypes: 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub>, and  
5-HT<sub>1F</sub>. The 5-HT<sub>1A</sub> receptor is the best known among the different 5-HT  
receptors and is widely distributed in the central nervous system (L.  
Lanfurney and M. Hamon, *Nuclear Medicine & Biology*, 27:429-435  
(2000)).

25    **[0004]**     Studies on the 5-HT<sub>1A</sub> receptor have shown potential roles in a  
variety of physiological processes including, neuroendocrine function,  
thermoregulation, vasoreactive headaches, sexual behavior, food intake,  
tooth-germ morphogenesis, immune function, aggression, depression and  
anxiety (J. R. Raymond, *et al.*, *Br. J. Pharmacol.*, 127:1751-1764 (1999)).  
30    Other studies have shown the potential use of 5-HT<sub>1A</sub> agonists in

glaucoma to lower intraocular pressure in the eye (N. N. Osborne, *et al.*, *Eye*, 14:454-463 (2000)). Recent studies have shown the involvement of 5-HT<sub>1A</sub> receptors in the transmission of nociceptive (pain) information in the spinal cord resulting from nerve injury or inflammation (Z.-Y. Liu, *et al.*, *Neuroscience*, 112(2):399-407 (2002)). Growing evidence suggests that the 5-HT<sub>1A</sub> receptor is important in learning and memory processes (A. Meneses, *Neurosci. Biobehav. Rev.*, 23:1111-1125 (1999)) and that 5-HT<sub>1A</sub> receptor antagonists may have utility in treating cognitive dysfunction associated with Alzheimer's disease (L. E. Schechter, *et al.*, *Curr. Pharm. Des.*, 8(2):139-145 (2002)). A 5-HT<sub>1A</sub> receptor agonist has shown a neuroprotective effect associated with its ability to inhibit ischemia-induced release of glutamate in the brain in a stroke model (I. Semkova, *et al.*, *Eur. J. Pharmacol.*, 359:251-260 (1998)).

[0005] Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG<sub>2</sub>, PGH<sub>2</sub> and PGE<sub>2</sub>, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (Cox). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (Cox-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

[0006] Compounds that selectively inhibit the cyclooxygenase-2 enzyme have been discovered. These compounds selectively inhibit the activity of Cox-2 to a greater extent than the activity of Cox-1. The Cox-2-selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, cyclooxygenase-2-selective inhibitors have shown great promise for use in therapies -- especially in therapies that require extended administration, such as for pain and inflammation control for arthritis. Additional information on the identification of cyclooxygenase-2-selective inhibitors can be found in: (1) Buttgerit, F. *et al.*, *Am. J. Med.*, 110(3 Suppl. 1):13-9 (2001); (2) Osiri, M. *et al.*, *Arthritis Care Res.*, 12(5):351-62 (1999); (3) Buttar, N.S. *et al.*, *Mayo Clin. Proc.*, 75(10):1027-38 (2000); (4) Wollheim, F. A., *Current Opin. Rheumatol.*, 13:193-201 (2001); (5) U.S. Patent Nos. 5,434,178 (1,3,5-trisubstituted pyrazole compounds); (6) 5,476,944 (derivatives of cyclic phenolic thioethers); (7) 5,643,933 (substituted sulfonylphenylheterocycles); 5,859,257 (isoxazole compounds); (8) 5,932,598 (prodrugs of benzenesulfonamide-containing Cox-2 inhibitors); (9) 6,156,781 (substituted pyrazolyl benzenesulfonamides); and (10) 6,110,960 (for dihydrobenzopyran and related compounds).

[0007] Cox-2 inhibitors have also been described for the treatment of cancer (WO98/16227) and for the treatment of tumors (See, EP 927,555, and Rozic *et al.*, *Int. J. Cancer*, 93(4):497 - 506 (2001)). Celecoxib, a selective inhibitor of Cox-2, exerted a potent inhibition of fibroblast growth factor-induced corneal angiogenesis in rats. (Masferrer *et al.*, *Proc. Am. Assoc. Cancer Research* 1999, 40: 396). WO 98/41511 describes 5-(4-sulphonyl-phenyl)-pyridazinone derivatives used for treating cancer. WO 98/41516 describes (methylsulphonyl)phenyl-2-(5H)-furanone derivatives that can be used in the treatment of cancer. Kalgutkar, A. S. *et al.*, *Curr. Drug Targets*, 2(1):79 - 106 (2001) suggest that Cox-2 selective inhibitors could be used to prevent or treat cancer by affecting tumor viability, growth, and metastasis. Masferrer *et al.*, in *Ann. NY Acad. Sci.*, 889:84 -

86 (1999) describe Cox-2 selective inhibitors as antiangiogenic agents with potential therapeutic utility in several types of cancers. The utility of Cox-2 inhibition in clinical cancer prevention was described by Lynch, P. M., in *Oncology*, 15(3):21 - 26 (2001), and Watanabe *et al.*, in *Biofactors* 2000, 12(1 - 4):129 - 133 (2000) described the potential of Cox-2 selective inhibitors for chemopreventive agents against colon cancer.

5 [0008] Additionally, various combination therapies using Cox-2 inhibitors with other selected combination regimens for the treatment of cancer have also been reported. See *e.g.*, FR 27 71 005 (compositions containing a cyclooxygenase-2 inhibitor and N- methyl-d-aspartate (NMDA) antagonist used to treat cancer and other diseases); WO 10 99/18960 (combination comprising a cyclooxygenase-2 inhibitor and an inducible nitric-oxide synthase inhibitor (iNOS) that can be used to treat colorectal and breast cancer); WO 99/13799 (combination of a 15 cyclooxygenase-2 inhibitor and an opioid analgesic); WO 97/36497 (combination comprising a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor useful in treating cancer); WO 97/29776 (composition comprising a cyclooxygenase-2 inhibitor in combination with a leukotriene B4 receptor antagonist and an immunosuppressive drug); 20 WO 97/29775 (use of a cyclooxygenase-2 inhibitor in combination with a leukotriene A4 hydrolase inhibitor and an immunosuppressive drug); WO 97/29774 (combination of a cyclooxygenase-2 inhibitor and prostaglandin or antiulcer agent useful in treating cancer); WO 97/11701 (combination comprising of a cyclooxygenase-2 inhibitor and a leukotriene B receptor 25 antagonist useful in treating colorectal cancer); WO 96/41645 (combination comprising a cyclooxygenase-2 inhibitor and leukotriene A hydrolase inhibitor); WO 96/03385 (3,4,-Di substituted pyrazole compounds given alone or in combination with NSAIDs, steroids, 5-LO inhibitors, LTB4 antagonists, or LTA4 hydrolase inhibitors for the treatment 30 of cancer); WO 98/47890 (substituted benzopyran derivatives that may be used alone or in combination with other active principles); WO 00/38730 (method of using cyclooxygenase-2 inhibitor and one or more

antineoplastic agents as a combination therapy in the treatment of neoplasia); Mann, M. *et al.*, *Gastroenterology*, 120(7):1713 - 1719 (2001) (combination treatment with Cox-2 and HER-2/neu inhibitors reduced colorectal carcinoma growth).

5 [0009] Other reports have indicated the Cox-2 selective inhibitors have cardiovascular applications. For example, Saito, T. *et al.*, in *Biochem. Biophys. Res. Comm.*, 273:772 - 775 (2000), reported that the inhibition of Cox-2 improves cardiac function in myocardial infarction. Ridker, P.M. *et al.*, in *The New England J. of Med.*, 336(14):973 - 979 (1997), raised the possibility that anti-inflammatory agents may have clinical benefits in preventing cardiovascular disease. In addition, Cox-2 selective inhibitors have been proposed for therapeutic use in cardiovascular disease when combined with modulation of inducible nitric oxide synthase (See, Baker, C. S. R. *et al.*, *Arterioscler. Thromb. Vasc. Biol.*, 19:646-655 (1999)), and with HMG-CoA reductase inhibitor (U.S. Patent No. 6,245,797).

10 [00010] Recent studies have shown that Cox-2 and its reaction products participate in ischemic injury in the human brain caused by stroke or other injury (C. Iadecola, *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 98(3):1294-1299 (2001)). A selective Cox-2 inhibitor has been shown to be neuroprotective, resulting in improvements in behavioral deficits caused by spinal cord ischemia (P. A. Lapchak, *et al.*, *Stroke*, 32:1220-1225 (2001)). Studies have shown that Cox-2 expression is elevated in Alzheimer's disease brains, is correlated with dementia, and causes detrimental alterations of the neuronal cell cycle (Xiang *et al.*, *Neurobiol. Aging*, 23:327-334 (2002)).

20 [00011] EP 1064967 describes the combination of 5-HT<sub>1A</sub> receptor agonists, caffeine, and either a Cox-2 inhibitor or NSAID for the treatment of migraine.

25 [00012] EP 1064966 describes the combination of a 5-HT<sub>1A</sub> receptor agonist, caffeine, and a Cox-2 inhibitor for the treatment of migraine.

[00013] EP 1064948 describes the combination of a 5-HT<sub>1A</sub> receptor antagonist, caffeine, and a Cox-2 inhibitor for the treatment of migraine.

[00014] EP 1051995 describes the combination of 5-HT<sub>1A</sub> receptor agonists and either a Cox-2 inhibitor or NSAID for the treatment of migraine.

[00015] EP 1051994 describes the combination of a 5-HT<sub>1A</sub> agonist and a Cox-2 inhibitor for the treatment of migraine.

[00016] EP 1051993 describes the combination of 5-HT<sub>1A</sub> receptor agonists and either a Cox-2 inhibitor or NSAID for the treatment of migraine.

[00017] US 20020077328 describes the combination of selective Cox-2 inhibitors and vasomodulator compounds for generalized pain and headache pain.

[00018] WO 0048583 describes the combination of 5-HT agonists with Cox-2 inhibitors for the treatment of migraine.

[00019] U.S. Patent Nos. 6,420,432, 6,413,961, 6,261,279, 6,254,585, 6,242,447, 6,210,394, 6,056,715, 5,860,950, 5,858,017, 5,820,583, and 5,800,385 describe various types of irrigation solution and a method for inhibition of pain and inflammation, where the solutions can contain a Cox-2 inhibitor and some type of serotonin agonist or 5-HT<sub>1A</sub> receptor agonist.

[00020] In U.S. Patent Publication No. 2002/0077328 A1, Hassan *et al.* disclose, among other things, a method for treatment of headache symptoms by administering a selective Cox-2 inhibitor and a vasomodulator, where the IC<sub>50</sub> of the combination for binding of 5TH<sub>1A</sub> [HT<sub>1A</sub>] receptors is at least about 250 nM.

[00021] A need remains, however, for an improved method of treating and preventing pain, inflammation or inflammation-related disorders, and also for treating and preventing neurologic disorders involving neurodegeneration. In particular, it would be useful to provide such a method by utilizing a combination of therapeutic agents that is more efficacious and safer than presently available methods.

### **SUMMARY OF THE INVENTION**

[00022] Briefly, therefore, the present invention is directed to a novel composition comprising a Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator.

5 [00023] The present invention is also directed to a novel method for the treatment or prevention of pain, inflammation, or inflammation-related disorder in a mammal in need thereof, comprising administering to the mammal a Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator.

10 [00024] The present invention is also directed to a novel pharmaceutical composition for the treatment or prevention of pain, inflammation, or inflammation-related disorder, the pharmaceutical composition comprising a Cox-2 inhibitor, a 5-HT<sub>1A</sub> receptor modulator, and a pharmaceutically-acceptable excipient.

15 [00025] The present invention is also directed to a novel kit that is suitable for use in the treatment or prevention of pain, inflammation, or inflammation-related disorder wherein the kit comprises a first dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a 5-HT<sub>1A</sub> receptor modulator, in quantities which comprise a therapeutically effective amount of the compounds for the treatment or prevention of pain, inflammation, or inflammation-related disorder.

20 [00026] The present invention is also directed to a novel method for the treatment or prevention of neurologic disease involving neurodegeneration in a mammal in need thereof, comprising administering to the mammal a Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator.

25 [00027] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of an improved method of treating or preventing pain, inflammation or inflammation-related disorders, and treatment or prevention of neurologic diseases involving neurodegeneration, the provision of such a method by utilizing a combination of therapeutic agents that is more efficacious and safer than

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methods and compositions that are presently available, and the provision of therapeutic combinations and methods for the prevention and treatment of pain, inflammation and inflammation-related disorders.

#### **DETAILED DESCRIPTION OF THE INVENTION**

- 5     **[00028]** In accordance with the present invention, it has been discovered that pain, inflammation, or inflammation-related disorders in a subject -- in particular, a mammal -- can be treated or prevented by a combination therapy method that involves administering to the subject an amount of a Cox-2 inhibitor and an amount of a 5-HT<sub>1A</sub> receptor
- 10     modulator. In preferred embodiments, the amount of the Cox-2 inhibitor and the amount of the 5-HT<sub>1A</sub> receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation or inflammation-related disorder in the subject.
- 15     **[00029]** Also disclosed herein is a composition comprising an amount of a Cox-2 inhibitor and an amount of a 5-HT<sub>1A</sub> receptor modulator wherein the amount of the Cox-2 inhibitor and the amount of the 5-HT<sub>1A</sub> receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation or inflammation-related disorder.
- 20     **[00030]** A component of the present invention is a Cox-2 inhibitor. The terms "cyclooxygenase-2 inhibitor", or "Cox-2 inhibitor", which can be used interchangeably herein, embrace compounds which inhibit the Cox-2 enzyme regardless of the degree of inhibition of the Cox-1 enzyme, and include pharmaceutically acceptable salts of those compounds. Thus, for
- 25     purposes of the present invention, a compound is considered a Cox-2 inhibitor irrespective of whether the compound inhibits the Cox-2 enzyme to an equal, greater, or lesser degree than the Cox-1 enzyme.
- 30     **[00031]** In one embodiment of the present invention, it is preferred that the Cox-2 inhibitor compound is a non-steroidal anti-inflammatory drug (NSAID). Therefore, preferred materials that can serve as the Cox-2 inhibitor of the present invention include non-steroidal anti-inflammatory

drug compounds, a pharmaceutically acceptable salt thereof, or a pure (-) or (+) optical isomeric form thereof.

[00032] Examples of NSAID compounds that are useful in the present invention include acemetacin, acetyl salicylic acid, alclofenac, alminoprofen, azapropazone, benorylate, benoxaprofen, bucloxic acid, 5 carprofen, choline magnesium trisalicylate, clidanac, clopinac, dapsone, diclofenac, diflunisal, droxicam, etodolac, fenoprofen, fenbufen, fenclofenec, fentiazac, floctafenine, flufenisal, flurbiprofen, (r)-flurbiprofen, (s)-flurbiprofen, furofenac, feprazone, flufenamic acid, fluprofen, ibufenac, 10 ibuprofen, indometacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, miroprofen, piroxicam, meloxicam, mefenamic, mefenamic acid, meclofenamic acid, meclofen, nabumetone, naproxen, niflumic acid, oxaprozin, oxipinac, oxyphenbutazone, phenylbutazone, podophyllotoxin derivatives, proglumetacin, pirofen, pirprofen, 15 prapoprofen, salicylic acid, salicylate, sudoxicam, suprofen, sulindac, tenoxicam, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, zidometacin, zomepirac, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

[00033] In a preferred embodiment, the Cox-2 inhibitor is a Cox-2 selective inhibitor. The term "Cox-2 selective inhibitor" embraces 20 compounds which selectively inhibit the Cox-2 enzyme over the Cox-1 enzyme, and also include pharmaceutically acceptable salts and prodrugs of those compounds.

[00034] In practice, the selectivity of a Cox-2 inhibitor varies depending 25 upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC<sub>50</sub> value for inhibition of Cox-1, divided by the IC<sub>50</sub> value for inhibition of Cox-2 (Cox-1 IC<sub>50</sub>/Cox-2 IC<sub>50</sub>). A Cox-2 selective inhibitor is 30 any inhibitor for which the ratio of Cox-1 IC<sub>50</sub> to Cox-2 IC<sub>50</sub> is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably

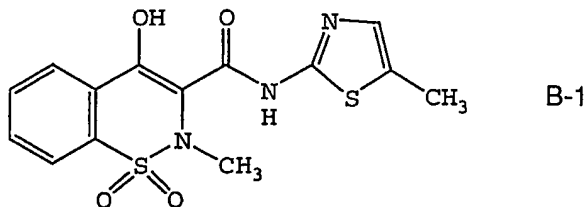
greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

5 [00035] As used herein, the term "IC<sub>50</sub>" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred Cox-2 selective inhibitors of the present invention have a Cox-2 IC<sub>50</sub> of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

[00036] Preferred Cox-2 selective inhibitors have a Cox-1 IC<sub>50</sub> of greater than about 1 μM, and more preferably of greater than 20 μM. 10 Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

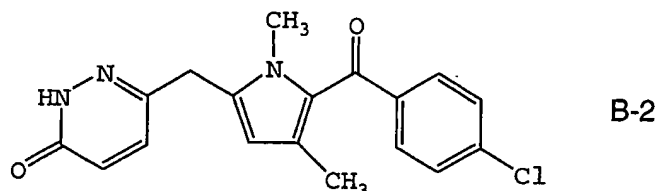
[00037] Also included within the scope of the present invention are compounds that act as prodrugs of Cox-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers 15 to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor valdecoxib. An example of a preferred 20 Cox-2 selective inhibitor prodrug is sodium parecoxib. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

[00038] The Cox-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or 25 prodrug thereof.



B-1

[00039] In another embodiment of the invention the Cox-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



[00040] As used herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; embraces linear or branched radicals having one to about twenty carbon atoms. Lower alkyl radicals have one to about ten carbon atoms. The number of carbon atoms can also be expressed as "C<sub>1</sub>-C<sub>5</sub>", for example. Examples of lower alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the like.

[00041] The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. The alkenyl radicals may be optionally substituted with groups such as those defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like.

[00042] The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups such as described below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-

methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

**[00043]** The term "oxo" means a single double-bonded oxygen.

5 **[00044]** The terms "hydrido", "-H", or "hydrogen", denote a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical, or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH<sub>2</sub> -) radical.

10 **[00045]** The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo alkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

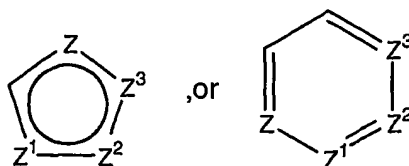
15 **[00046]** The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

20 **[00047]** The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and diaikoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy.

25 **[00048]** The term "aryl", whether used alone or with other terms, means 30 a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner, or may be fused. The term "aryl" embraces aromatic radicals such as phenyl,

naphthyl, tetrahydronaphthyl, indane, and biphenyl. The term “heterocyclyl” means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms are replaced by N, S, P, or O. This includes, for example, structures such as:

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where Z, Z<sup>1</sup>, Z<sup>2</sup>, or Z<sup>3</sup> is C, S, P, O, or N, with the proviso that one of Z, Z<sup>1</sup>, Z<sup>2</sup>, or Z<sup>3</sup> is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z<sup>1</sup>, Z<sup>2</sup>, or Z<sup>3</sup> only when each is C. The term “heterocycle” also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others.

**[00049]** The term “heteroaryl” embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals include thienyl, pyrrolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranal, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

**[00050]** The term “sulfonyl”, whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals –SO<sub>2</sub>–. “Alkylsulfonyl”, embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term “arylsulfonyl” embraces sulfonyl radicals substituted with an aryl radical. The term “aminosulfonyl” denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide (–SO<sub>2</sub>–NH<sub>2</sub>).

[00051] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $\text{--CO}_2\text{--H}$ . The term "carboxyalkyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical. The term "carbonyl", whether used  
5 alone or with other terms, such as "alkylcarbonyl", denotes  $\text{--(C=O)--}$ . The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is  $\text{CH}_3\text{--(CO)--}$ . The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a  
10 carbonyl ( $\text{C=O}$ ) radical. Examples of such "alkoxycarbonyl" radicals include  $(\text{CH}_3)_3\text{C--O--C=O--}$  and  $\text{--(O=C)--OCH}_3$ . The term "amino", whether used alone or with other terms, such as "aminocarbonyl", denotes  $\text{--NH}_2$ .

[00052] The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The terms "aralkyl",  
15 or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl  
20 cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

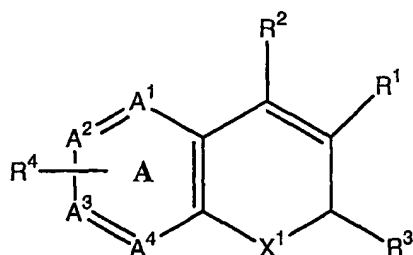
[00053] The term "alkylthio" embraces radicals containing a linear or  
25 branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio,  $(\text{CH}_3\text{--S--})$ . The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent  $\text{--S(=O)--}$  atom. The term "acyl", whether used alone, or within a term such as "acylamino",  
30 denotes a radical provided by the residue after removal of hydroxyl from an organic acid.

[00054] The term "cyano", used either alone or with other terms, such as "cyanoalkyl", refers to  $C\equiv N$ . The term "nitro" denotes  $-NO_2$ .

[00055] In one embodiment of the invention the Cox-2 selective inhibitor is of the chromene/chroman structural class, which encompasses  
 5 substituted benzopyrans or substituted benzopyran analogs, as well as substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the general Formulas I, II, III, IV, V, and VI, shown below, and including, by way of non-limiting example, the structures disclosed in Table 1, and the diastereomers, enantiomers,  
 10 racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00056] Benzopyrans that can serve as a Cox-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent Nos. 6,271,253 and 6,492,390. One such class of compounds is defined by the general formula shown below in formula I:

15



I

wherein  $X^1$  is selected from O, S,  $CR^b R^c$  and  $NR^a$ ;

wherein  $R^a$  is selected from hydrido,  $C_1 - C_3$  -alkyl, (optionally substituted phenyl)- $C_1 - C_3$  -alkyl, acyl and carboxy- $C_1 - C_6$  -alkyl;

20 wherein each of  $R^b$  and  $R^c$  is independently selected from hydrido,  $C_1 - C_3$  -alkyl, phenyl- $C_1 - C_3$  -alkyl,  $C_1 - C_3$  -perfluoroalkyl, chloro,  $C_1 - C_6$  -alkylthio,  $C_1 - C_6$  -alkoxy, nitro, cyano and cyano- $C_1 - C_3$  -alkyl; or wherein  $CR^b R^c$  forms a 3-6 membered cycloalkyl ring;

25 wherein  $R^1$  is selected from carboxyl, aminocarbonyl,  $C_1 - C_6$  -alkylsulfonylaminocarbonyl and  $C_1 - C_6$  -alkoxycarbonyl;

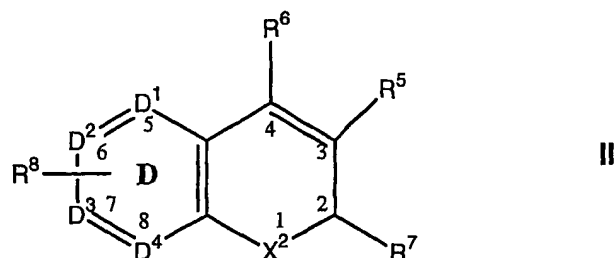
wherein  $R^2$  is selected from hydrido, phenyl, thienyl,  $C_1 - C_6$  -alkyl and  $C_2 - C_6$  -alkenyl;



wherein  $R^3$  is selected from  $C_1-C_3$ -perfluoroalkyl, chloro,  $C_1-C_6$ -alkylthio,  $C_1-C_6$ -alkoxy, nitro, cyano and cyano- $C_1-C_3$ -alkyl;  
 wherein  $R^4$  is one or more radicals independently selected from hydrido,  
 halo,  $C_1-C_6$ -alkyl,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl, halo- $C_2-C_6$ -  
 5 alkynyl, aryl- $C_1-C_3$ -alkyl, aryl- $C_2-C_6$ -alkynyl, aryl- $C_2-C_6$ -alkenyl,  $C_1-C_6$ -alkoxy, methylenedioxy,  $C_1-C_6$ -alkylthio,  $C_1-C_6$ -alkylsulfinyl,  
 aryloxy, arylthio, arylsulfinyl, heteroaryloxy,  $C_1-C_6$ -alkoxy- $C_1-C_6$ -alkyl,  
 aryl- $C_1-C_6$ -alkyloxy, heteroaryl- $C_1-C_6$ -alkyloxy, aryl- $C_1-C_6$ -alkoxy- $C_1$ -  
 $C_6$ -alkyl,  $C_1-C_6$ -haloalkyl,  $C_1-C_6$ -haloalkoxy,  $C_1-C_6$ -haloalkylthio,  
 10  $C_1-C_6$ -haloalkylsulfinyl,  $C_1-C_6$ -haloalkylsulfonyl,  $C_1-C_3$ -(haloalkyl- $C_1-C_3$ -hydroxyalkyl,  $C_1-C_6$ -hydroxyalkyl, hydroxyimino- $C_1-C_6$ -alkyl,  $C_1-C_6$ -alkylamino, arylamino, aryl- $C_1-C_6$ -alkylamino, heteroarylamino,  
 heteroaryl- $C_1-C_6$ -alkylamino, nitro, cyano, amino, aminosulfonyl,  $C_1-C_6$ -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl- $C_1-C_6$ -alkylaminosulfonyl, heteroaryl- $C_1-C_6$ -alkylaminosulfonyl,  
 15 heterocyclisulfonyl,  $C_1-C_6$ -alkylsulfonyl, aryl- $C_1-C_6$ -alkylsulfonyl,  
 optionally substituted aryl, optionally substituted heteroaryl, aryl- $C_1-C_6$ -alkylcarbonyl, heteroaryl- $C_1-C_6$ -alkylcarbonyl, heteroarylcarbonyl,  
 arylcarbonyl, aminocarbonyl,  $C_1-C_1$ -alkoxycarbonyl, formyl,  $C_1-C_6$ -  
 20 haloalkylcarbonyl and  $C_1-C_6$ -alkylcarbonyl; and  
 wherein the A ring atoms  $A^1$ ,  $A^2$ ,  $A^3$  and  $A^4$  are independently selected  
 from carbon and nitrogen with the proviso that at least two of  $A^1$ ,  $A^2$ ,  $A^3$   
 and  $A^4$  are carbon;  
 or wherein  $R^4$  together with ring A forms a radical selected from naphthyl,  
 25 quinolyl, isoquinolyl, quinoliziny, quinoxaliny and dibenzofuryl;  
 or an isomer or pharmaceutically acceptable salt thereof.

**[00057]** Another class of benzopyran derivatives that can serve as the  
 Cox-2 selective inhibitor of the present invention includes compounds  
 having the structure of formula II:

30



wherein  $X^2$  is selected from O, S,  $CR^cR^b$  and  $NR^a$ ;

wherein R<sup>a</sup> is selected from hydrido, C<sub>1</sub>–C<sub>3</sub>–alkyl, (optionally substituted phenyl)–C<sub>1</sub>–C<sub>3</sub>–alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy–C<sub>1</sub>–C<sub>6</sub>–alkyl;

wherein each of  $R^b$  and  $R^c$  is independently selected from hydrido,  $C_1-C_3$ -alkyl, phenyl- $C_1-C_3$ -alkyl,  $C_1-C_3$ -perfluoroalkyl, chloro,  $C_1-C_6$ -alkylthio,  $C_1-C_6$ -alkoxy, nitro, cyano and cyano- $C_1-C_3$ -alkyl; or wherein  $CR^cR^b$  form a cyclopropyl ring;

10 wherein R<sup>5</sup> is selected from carboxyl, aminocarbonyl, C<sub>1</sub>–C<sub>6</sub>–alkylsulfonylaminocarbonyl and C<sub>1</sub>–C<sub>6</sub>–alkoxycarbonyl;

wherein R<sup>6</sup> is selected from hydrido, phenyl, thienyl, C<sub>2</sub>–C<sub>6</sub>–alkynyl and C<sub>2</sub>–C<sub>6</sub>–alkenyl;

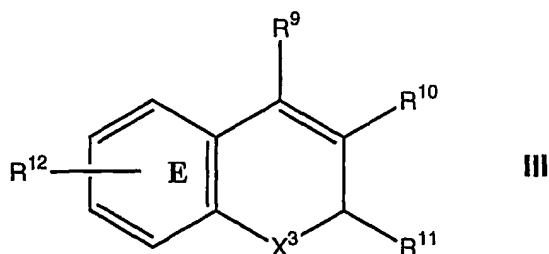
15 wherein R<sup>7</sup> is selected from C<sub>1</sub>–C<sub>3</sub>–perfluoroalkyl, chloro, C<sub>1</sub>–C<sub>6</sub>–alkylthio, C<sub>1</sub>–C<sub>6</sub>–alkoxy, nitro, cyano and cyano-C<sub>1</sub>–C<sub>3</sub>–alkyl;

wherein R<sup>8</sup> is one or more radicals independently selected from hydrido, halo, C<sub>1</sub>–C<sub>6</sub>–alkyl, C<sub>2</sub>–C<sub>6</sub>–alkenyl, C<sub>2</sub>–C<sub>6</sub>–alkynyl, halo-C<sub>2</sub>–C<sub>6</sub>–alkynyl, aryl-C<sub>1</sub>–C<sub>3</sub>–alkyl, aryl-C<sub>2</sub>–C<sub>6</sub>–alkynyl, aryl-C<sub>2</sub>–C<sub>6</sub>–alkenyl, C<sub>1</sub>–C<sub>6</sub>–alkoxy, methylenedioxy, C<sub>1</sub>–C<sub>6</sub>–alkylthio, C<sub>1</sub>–C<sub>6</sub>–alkylsulfanyl, —O(CF<sub>2</sub>)<sub>2</sub>—, aryloxy, arylthio, arylsulfanyl, heteroaryloxy, C<sub>1</sub>–C<sub>6</sub>–alkoxy-C<sub>1</sub>–C<sub>6</sub>–alkyl, aryl-C<sub>1</sub>–C<sub>6</sub>–alkoxy, heteroaryl-C<sub>1</sub>–C<sub>6</sub>–alkoxy, aryl-C<sub>1</sub>–C<sub>6</sub>–alkoxy-C<sub>1</sub>–C<sub>6</sub>–alkyl, C<sub>1</sub>–C<sub>6</sub>–haloalkyl, C<sub>1</sub>–C<sub>6</sub>–haloalkoxy, C<sub>1</sub>–C<sub>6</sub>–haloalkylthio, C<sub>1</sub>–C<sub>6</sub>–haloalkylsulfanyl, C<sub>1</sub>–C<sub>6</sub>–haloalkylsulfonyl, C<sub>1</sub>–C<sub>3</sub>–(haloalkyl-C<sub>1</sub>–C<sub>3</sub>–hydroxyalkyl), C<sub>1</sub>–C<sub>6</sub>–hydroxyalkyl, hydroxyimino-C<sub>1</sub>–C<sub>6</sub>–alkyl, C<sub>1</sub>–C<sub>6</sub>–alkylamino, arylamino, aryl-C<sub>1</sub>–C<sub>6</sub>–alkylamino, heteroarylamino, heteroaryl-C<sub>1</sub>–C<sub>6</sub>–alkylamino, nitro, cyano, amino, aminosulfonyl, C<sub>1</sub>–C<sub>6</sub>–alkylaminosulfonyl, arylaminosulfonyl,

heteroarylaminosulfonyl, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylaminosulfonyl, heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkylaminosulfonyl, heterocyclisulfonyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, formyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl and C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl; and wherein the D ring atoms D<sup>1</sup>, D<sup>2</sup>, D<sup>3</sup> and D<sup>4</sup> are independently selected from carbon and nitrogen with the proviso that at least two of D<sup>1</sup>, D<sup>2</sup>, D<sup>3</sup> and D<sup>4</sup> are carbon; or

wherein R<sup>8</sup> together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinoliziny, quinoxaliny and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

**[00058]** Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula III:



wherein X<sup>3</sup> is selected from the group consisting of O or S or NR<sup>a</sup>;

wherein R<sup>a</sup> is alkyl;

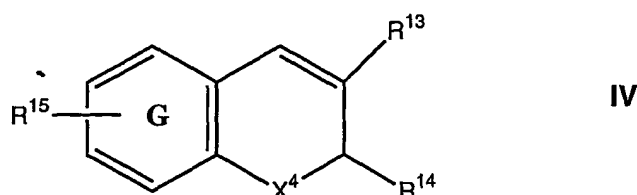
wherein R<sup>9</sup> is selected from the group consisting of H and aryl;

wherein R<sup>10</sup> is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

wherein R<sup>11</sup> is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein  $R^{12}$  is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcabonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or  
 10 wherein  $R^{12}$  together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

**[00059]** A related class of compounds useful as Cox-2 selective  
 15 inhibitors in the present invention is described by Formulas IV and V below:

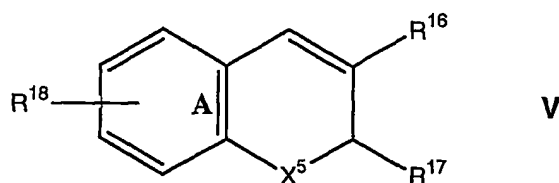


wherein  $X^4$  is selected from O or S or  $NR^a$ ;  
 20 wherein  $R^a$  is alkyl;  
 wherein  $R^{13}$  is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;  
 wherein  $R^{14}$  is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and  
 25 wherein  $R^{15}$  is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino,

heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl,  
alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl,  
aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl,  
alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl,  
5 aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and  
alkylcarbonyl;

or wherein  $R^{15}$  together with ring G forms a naphthyl radical;  
or an isomer or pharmaceutically acceptable salt thereof.

[00060] Formula V is:



wherein:

$X^5$  is selected from the group consisting of O or S or  $NR^b$ ;

$R^b$  is alkyl;

$R^{16}$  is selected from the group consisting of carboxyl, aminocarbonyl,  
15 alkylsulfonylaminocarbonyl and alkoxycarbonyl;

$R^{17}$  is selected from the group consisting of haloalkyl, alkyl, aralkyl,  
cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl  
each is independently optionally substituted with one or more radicals  
selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

20  $R^{18}$  is one or more radicals selected from the group consisting of hydrido,  
halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy,  
heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino,  
aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino,  
aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl,  
25 heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl,  
heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally  
substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl,

aminocarbonyl, and alkylcarbonyl; or wherein  $R^{18}$  together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

**[00061]** The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

$X^5$  is selected from the group consisting of oxygen and sulfur;

$R^{16}$  is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

$R^{17}$  is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

$R^{18}$  is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein  $R^{18}$  together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

**[00062]** The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

$X^5$  is selected from the group consisting of oxygen and sulfur;

$R^{16}$  is carboxyl;

$R^{17}$  is lower haloalkyl; and

$R^{18}$  is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower

aralkylcarbonyl, and lower alkylcarbonyl; or wherein  $R^{18}$  together with ring A forms a naphthyl radical;  
or an isomer or pharmaceutically acceptable salt thereof.

[00063] The Cox-2 selective inhibitor may also be a compound of  
5 Formula V, wherein:

$X^5$  is selected from the group consisting of oxygen and sulfur;

$R^{16}$  is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

10  $R^{17}$  is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

15  $R^{18}$  is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropoxy, *tert*butyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or  
20 wherein  $R^2$  together with ring A forms a naphthyl radical;  
or an isomer or pharmaceutically acceptable salt thereof.

25 [00064] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

$X^5$  is selected from the group consisting of oxygen and sulfur;

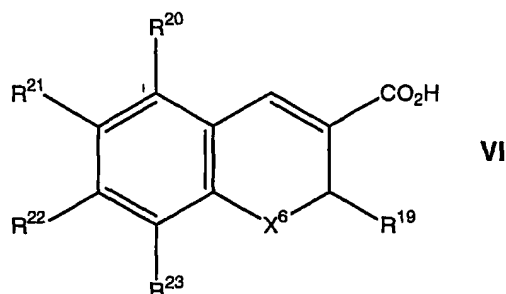
$R^{16}$  is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

30  $R^{17}$  is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

$R^{18}$  is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein  $R^{18}$  together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

**[00065]** The Cox-2 selective inhibitor of the present invention can also be a compound having the structure of Formula VI:



wherein:

$X^6$  is selected from the group consisting of O and S;

$R^{19}$  is lower haloalkyl;

$R^{20}$  is selected from the group consisting of hydrido, and halo;

$R^{21}$  is selected from the group consisting of hydrido, halo, lower alkyl,

lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower

dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl,

lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing

heterocyclosulfonyl, and 6-membered nitrogen-containing

heterocyclosulfonyl;

$R^{22}$  is selected from the group consisting of hydrido, lower alkyl, halo,

lower alkoxy, and aryl; and



$R^{23}$  is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl; or an isomer or prodrug thereof.

[00066] The Cox-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

$X^6$  is selected from the group consisting of O and S;

$R^{19}$  is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

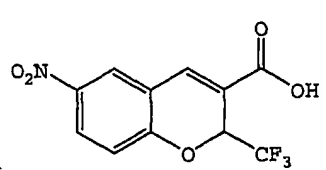
$R^{20}$  is selected from the group consisting of hydrido, chloro, and fluoro;

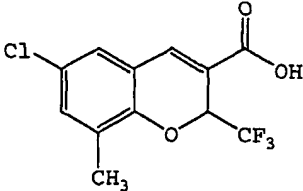
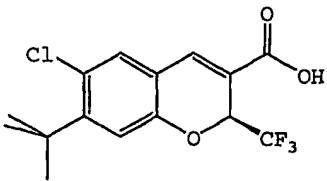
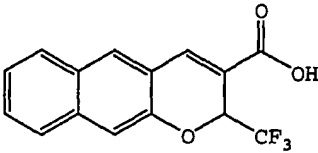
$R^{21}$  is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

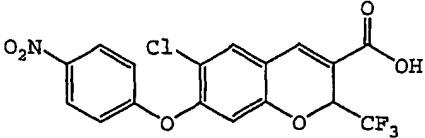
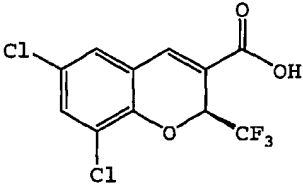
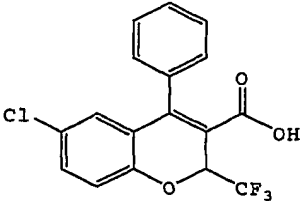
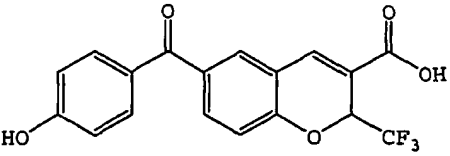
$R^{22}$  is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

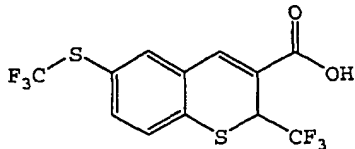
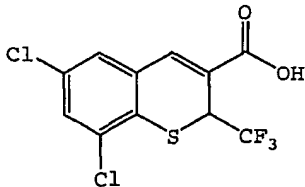
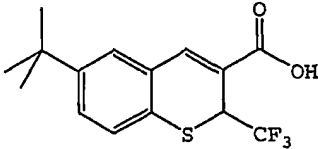
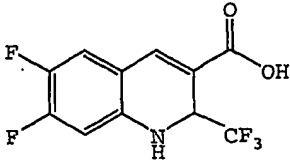
$R^{23}$  is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl; or an isomer or prodrug thereof.

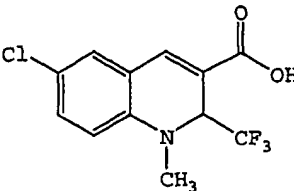
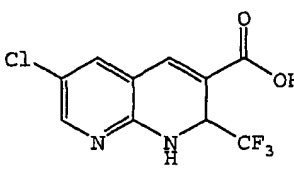
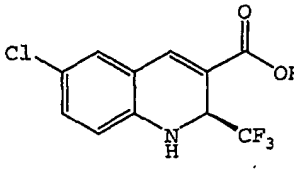
Table 1. Examples of Chromene Cox-2 Selective Inhibitors

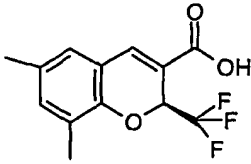
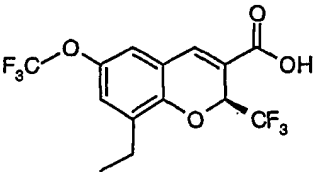
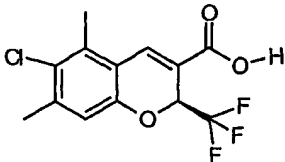
| <u>Compound Number</u> | <u>Structural Formula</u>   |
|------------------------|---|
| B-3                    |  <p>6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid</p> |

| <u>Compound Number</u> | <u>Structural Formula</u>  |
|------------------------|--|
| B-4                    |  <p>6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid</p>                      |
| B-5                    |  <p>((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p> |
| B-6                    |  <p>2-Trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid</p>                               |

| <u>Compound<br/>Number</u> | <u>Structural Formula</u>   |
|----------------------------|---|
| B-7                        |  <p>6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p> |
| B-8                        |  <p>((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p>          |
| B-9                        |  <p>6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid</p>         |
| B-10                       |  <p>6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p>      |

| <u>Compound Number</u> | <u>Structural Formula</u>   |
|------------------------|---|
| B-11                   |  <p>2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid</p> |
| B-12                   |  <p>6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid</p>               |
| B-13                   |  <p>6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid</p>   |
| B-14                   |  <p>6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p>           |

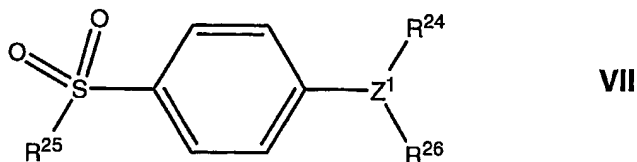
| <u>Compound Number</u> | <u>Structural Formula</u>   |
|------------------------|---|
| B-15                   |  <p>6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p>  |
| B-16                   |  <p>6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid</p> |
| B-17                   |  <p>((S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p>    |

| <u>Compound Number</u> | <u>Structural Formula</u>  |
|------------------------|--|
| B-18                   |  <p data-bbox="706 663 1279 720">(2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid</p>                   |
| B-19                   |  <p data-bbox="698 1005 1291 1062">(2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid</p> |
| B-20                   |  <p data-bbox="662 1297 1328 1354">(2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid</p>      |

[00067] In preferred embodiments the chromene Cox-2 inhibitor is selected from (S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-6-chloro-8-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6-chloro-5,7-

dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, and mixtures thereof.

[00068] In a preferred embodiment of the invention the Cox-2 inhibitor can be selected from the class of tricyclic Cox-2 selective inhibitors represented by the general structure of formula VII:



wherein:

- 10  $Z^1$  is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;
- $R^{24}$  is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein  $R^{24}$  is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfanyl, halo, alkoxy and alkylthio;
- 15  $R^{25}$  is selected from the group consisting of methyl or amino; and
- 20  $R^{26}$  is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N- arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N- arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amino,
- 25

aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

5 or a prodrug thereof.

**[00069]** In a preferred embodiment of the invention the Cox-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-21), valdecoxib (B-22), deracoxib (B-23), rofecoxib (B-24), etoricoxib (MK-663; B-25), JTE-522 (B-26), or prodrugs thereof.

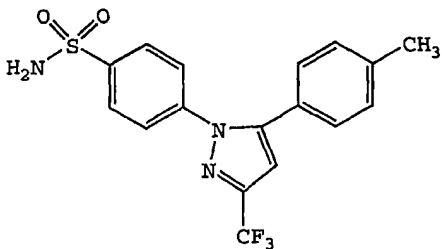
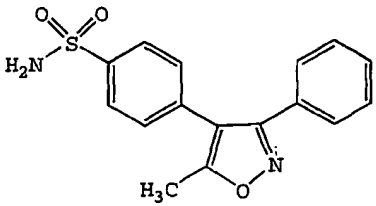
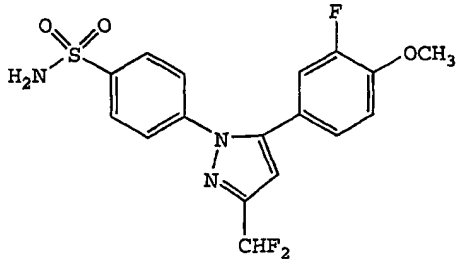
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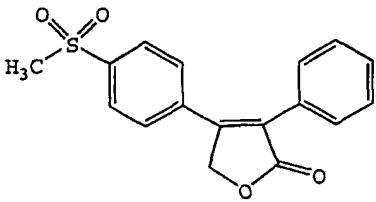
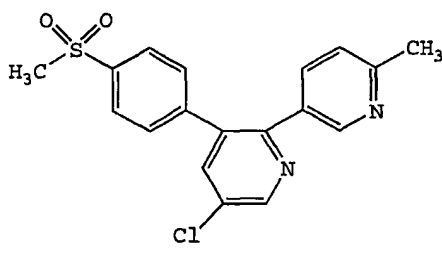
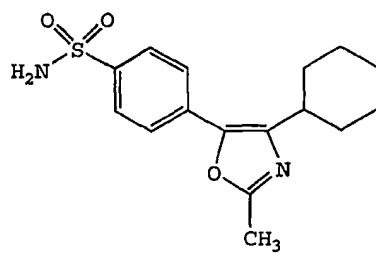
**[00070]** Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

15



Table 2. Examples of Tricyclic COX-2 Selective Inhibitors

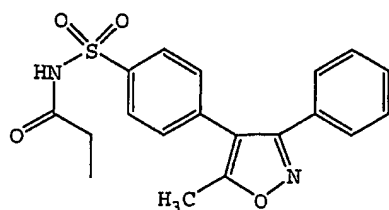
| <u>Compound Number</u> | <u>Structural Formula</u>   |
|------------------------|---|
| B-21                   | <br><chem>CC1=CC=C(C=C1)c2nc(C(F)(F)F)c(n2)Nc3ccc(S(=O)(=O)N)cc3</chem> |
| B-22                   | <br><chem>CC1=C(C(=C2C(=C1)N=CO2)c3ccc(S(=O)(=O)N)cc3)c4ccccc4</chem>  |
| B-23                   | <br><chem>COc1cc(F)ccc1c2cc(C(F)F)c(n2)Nc3ccc(S(=O)(=O)N)cc3</chem>   |

| <u>Compound Number</u> | <u>Structural Formula</u>  |
|------------------------|--|
| B-24                   |    |
| B-25                   |   |
| B-26                   |  |

[00071] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

- 5 [00072] In a preferred embodiment, parecoxib (See, U.S. Patent No. 5,932,598), having the structure shown in B-27, and which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor

valdecoxib, B-22, (See, U.S. Patent No. 5,633,272), may be advantageously employed as the Cox-2 inhibitor of the present invention.



B-27

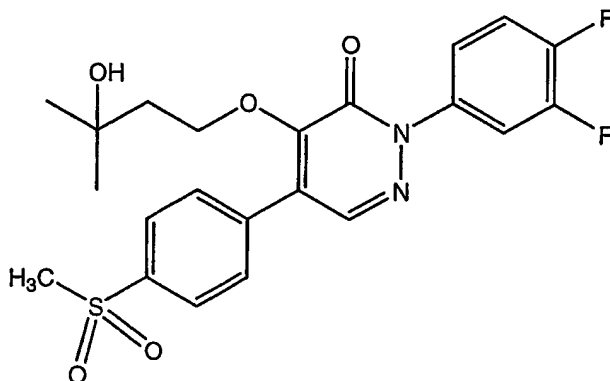
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[00073] A preferred form of parecoxib is sodium parecoxib.

[00074] Another tricyclic Cox-2 selective inhibitor useful in the present invention is the compound ABT-963, having the formula B-28 shown below, that has been previously described in International Publication

10

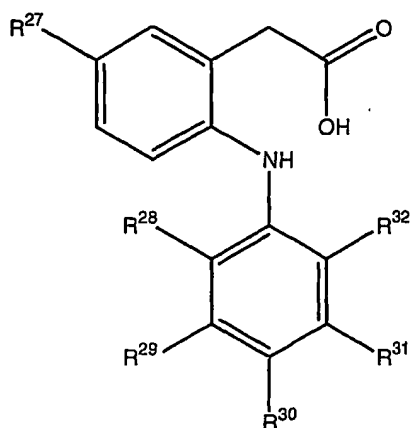
Number WO 00/24719.



B-28

[00075] In a further embodiment of the invention, the Cox-2 inhibitor can be selected from the class of phenylacetic acid derivative Cox-2 selective inhibitors represented by the general structure of formula VIII:

15



VIII

wherein:

$R^{27}$  is methyl, ethyl, or propyl;

5  $R^{28}$  is chloro or fluoro;

$R^{29}$  is hydrogen, fluoro, or methyl;

$R^{30}$  is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxyl;

$R^{31}$  is hydrogen, fluoro, or methyl; and

$R^{32}$  is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

10 provided that  $R^{28}$ ,  $R^{29}$ ,  $R^{30}$  and  $R^{31}$  are not all fluoro when  $R^{27}$  is ethyl and  $R^{30}$  is H.

[00076] An exemplary phenylacetic acid derivative Cox-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in formula VIII,

15 wherein:

$R^{27}$  is ethyl;

$R^{28}$  and  $R^{30}$  are chloro;

$R^{29}$  and  $R^{31}$  are hydrogen; and

$R^{32}$  is methyl.

20 [00077] Another phenylacetic acid derivative Cox-2 selective inhibitor is a compound that has the structure shown in formula VIII,

wherein:

$R^{27}$  is propyl;

$R^{28}$  and  $R^{30}$  are chloro;

$R^{29}$  and  $R^{31}$  are methyl; and

$R^{32}$  is ethyl.

[00078] Another phenylacetic acid derivative Cox-2 selective inhibitor that is disclosed in WO 02/20090 is a compound that is referred to as  
 5 COX-189 (also termed lumiracoxib; CAS Reg. No. 220991-20-8), having the structure shown in formula VIII,

wherein:

$R^{27}$  is methyl;

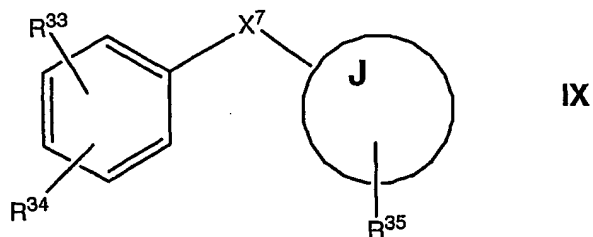
$R^{28}$  is fluoro;

10  $R^{32}$  is chloro; and

$R^{29}$ ,  $R^{30}$ , and  $R^{31}$  are hydrogen.

[00079] Compounds having a structure similar to that shown in formula VIII, that can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,451,858, 6,310,099,  
 15 6,291,523, and 5,958,978.

[00080] Other Cox-2 selective inhibitors that can be used in the present invention have the general structure shown in formula IX, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



20

wherein:

$X^7$  is O; J is 1-phenyl;  $R^{33}$  is 2-NHSO<sub>2</sub>CH<sub>3</sub>;  $R^{34}$  is 4-NO<sub>2</sub>; and there is no  $R^{35}$  group, (nimesulide), or

$X^7$  is O; J is 1-oxo-inden-5-yl;  $R^{33}$  is 2-F;  $R^{34}$  is 4-F; and  $R^{35}$  is 6-NHSO<sub>2</sub>CH<sub>3</sub>, (flosulide); or  
 25

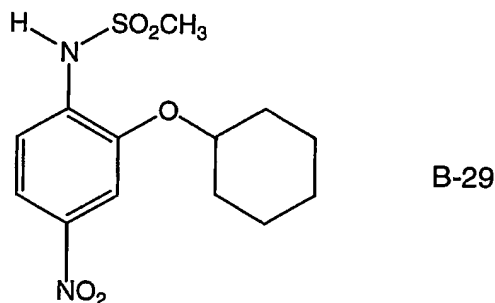
$X^7$  is O; J is cyclohexyl;  $R^{33}$  is 2-NHSO<sub>2</sub>CH<sub>3</sub>;  $R^{34}$  is 5-NO<sub>2</sub>; and there is no  $R^{35}$  group, (NS-398); or

$X^7$  is S; J is 1-oxo-inden-5-yl;  $R^{33}$  is 2-F;  $R^{34}$  is 4-F; and  $R^{35}$  is 6-N<sup>+</sup>SO<sub>2</sub>CH<sub>3</sub> · Na<sup>+</sup>, (L-745337); or

5  $X^7$  is S; J is thiophen-2-yl;  $R^{33}$  is 4-F; there is no  $R^{34}$  group; and  $R^{35}$  is 5-NHSO<sub>2</sub>CH<sub>3</sub>, (RWJ-63556); or

$X^7$  is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl;  $R^{33}$  is 3-F;  $R^{34}$  is 4-F; and  $R^{35}$  is 4-(p-SO<sub>2</sub>CH<sub>3</sub>)C<sub>6</sub>H<sub>4</sub>, (L-784512).

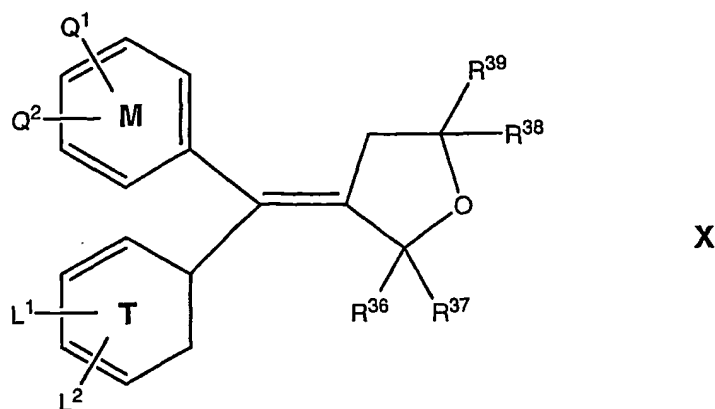
10 **[00081]** The Cox-2 selective inhibitor NS-398, also known as N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (CAS RN 123653-11-2), having a structure as shown below in formula B-29, has been described in, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res.*, 90(4):406 – 412 (1999).



15

**[00082]** An evaluation of the anti-inflammatory activity of the Cox-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther* 282, 1094-1101 (1997).

20 **[00083]** Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula X:



wherein:

the rings T and M independently are a phenyl radical, a naphthyl radical, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q<sup>1</sup>, Q<sup>2</sup>, L<sup>1</sup> or L<sup>2</sup> is an —S(O)<sub>n</sub>—R group, in which n is an integer equal to 0, 1 or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an —SO<sub>2</sub>NH<sub>2</sub> group;

and is located in the para position,

the others independently being a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a trifluoromethyl radical, or a lower O-alkyl radical having 1 to 6 carbon atoms, or Q<sup>1</sup> and Q<sup>2</sup> or L<sup>1</sup> and L<sup>2</sup> are a methylenedioxy group; and

R<sup>36</sup>, R<sup>37</sup>, R<sup>38</sup> and R<sup>39</sup> independently are a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R<sup>36</sup>, R<sup>37</sup> or R<sup>38</sup>, R<sup>39</sup> are an oxygen atom; or

R<sup>36</sup>, R<sup>37</sup> or R<sup>38</sup>, R<sup>39</sup>, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

[00084] Particular diarylmethylidenefuran derivatives that can serve as the Cox-2 selective inhibitor of the present invention include, for example, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

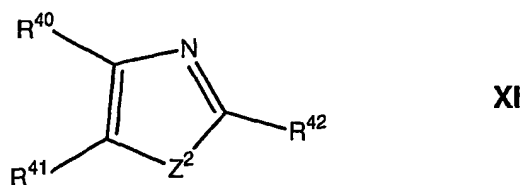
5 [00085] Other Cox-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256),  
10 BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474  
15 (Shionogi).

[00086] Compounds that may act as Cox-2 selective inhibitors of the present invention include multibinding compounds containing from 2 to 10 ligands covalently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

20 [00087] Conjugated linoleic, as described in U.S. Patent No. 6,077,868, is useful as a Cox-2 selective inhibitor in the present invention.

[00088] Compounds that can serve as a Cox-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such  
25 heterocyclic aromatic oxazole compounds have the formula shown below in formula XI:



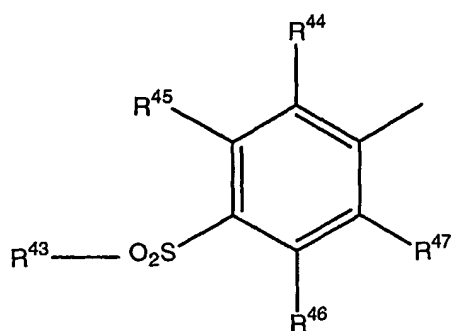


wherein:

Z<sup>2</sup> is an oxygen atom;

one of R<sup>40</sup> and R<sup>41</sup> is a group of the formula

5



wherein:

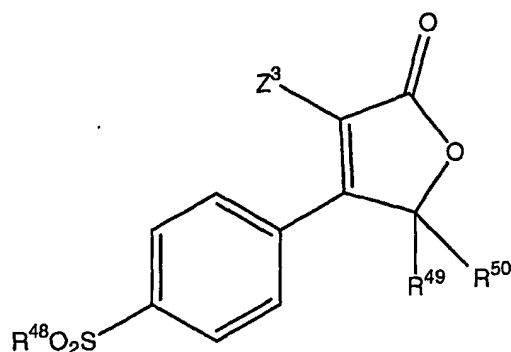
R<sup>43</sup> is lower alkyl, amino or lower alkylamino; and

10 R<sup>44</sup>, R<sup>45</sup>, R<sup>46</sup> and R<sup>47</sup> are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxyl or amino, provided that at least one of R<sup>44</sup>, R<sup>45</sup>, R<sup>46</sup> and R<sup>47</sup> is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

15 R<sup>30</sup> is a lower alkyl or a halogenated lower alkyl, and a pharmaceutically acceptable salt thereof.

[00089] Cox-2 selective inhibitors that are useful in the method and compositions of the present invention include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by

20 formula XII:



XII

wherein:

$Z^3$  is selected from the group consisting of linear or branched  $C_1 - C_6$  alkyl, linear or branched  $C_1 - C_6$  alkoxy, unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of hydrogen, halo,  $C_1 - C_3$  alkoxy, CN,  $C_1 - C_3$  fluoroalkyl  $C_1 - C_3$  alkyl, and  $-CO_2 H$ ;

$R^{48}$  is selected from the group consisting of  $NH_2$  and  $CH_3$ ,

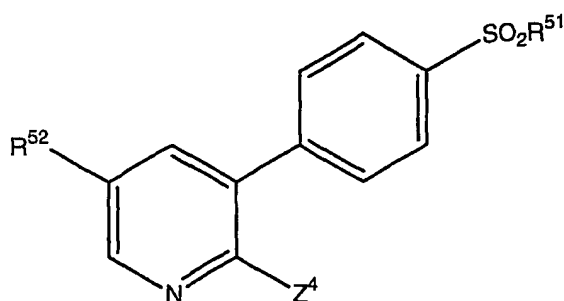
$R^{49}$  is selected from the group consisting of  $C_1 - C_6$  alkyl unsubstituted or substituted with  $C_3 - C_6$  cycloalkyl, and  $C_3 - C_6$  cycloalkyl;

$R^{50}$  is selected from the group consisting of:

$C_1 - C_6$  alkyl unsubstituted or substituted with one, two or three fluoro atoms, and  $C_3 - C_6$  cycloalkyl;

with the proviso that  $R^{49}$  and  $R^{50}$  are not the same.

**[00090]** Pyridines that are described in U.S. Patent Nos. 6,596,736, 6,369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and can serve as Cox-2 selective inhibitors of the present invention, have the general formula described by formula **XIII**:



XIII

wherein:

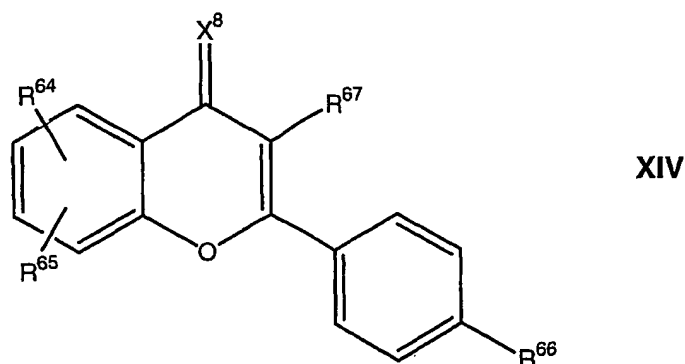
$R^{51}$  is selected from the group consisting of  $CH_3$ ,  $NH_2$ ,  $NHC(O)CF_3$ , and  $NHCH_3$ ;

$Z^4$  is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof), wherein the substituents are chosen from the group consisting of hydrogen, halo,  $C_1-C_6$  alkoxy,  $C_1-C_6$  alkylthio, CN,  $C_1-C_6$  alkyl,  $C_1-C_6$  fluoroalkyl,  $N_3$ ,  $-CO_2R^{53}$ , hydroxyl,  $-C(R^{54})(R^{55})-OH$ ,  $-C_1-C_6$  alkyl- $CO_2-R^{56}$ ,  $C_1-C_6$  fluoroalkoxy;

$R^{52}$  is chosen from the group consisting of: halo,  $C_1-C_6$  alkoxy,  $C_1-C_6$  alkylthio, CN,  $C_1-C_6$  alkyl,  $C_1-C_6$  fluoroalkyl,  $N_3$ ,  $-CO_2R^{57}$ , hydroxyl,  $-C(R^{58})(R^{59})-OH$ ,  $-C_1-C_6$  alkyl- $CO_2-R^{60}$ ,  $C_1-C_6$  fluoroalkoxy,  $NO_2$ ,  $NR^{61}R^{62}$ , and  $NHCOR^{63}$ ;

$R^{53}$ ,  $R^{54}$ ,  $R^{55}$ ,  $R^{56}$ ,  $R^{57}$ ,  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$ ,  $R^{61}$ ,  $R^{62}$ , and  $R^{63}$ , are each independently chosen from the group consisting of hydrogen and  $C_1-C_6$  alkyl; or  $R^{54}$  and  $R^{55}$ ,  $R^{58}$  and  $R^{59}$ , or  $R^{61}$  and  $R^{62}$  together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

**[00091]** Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



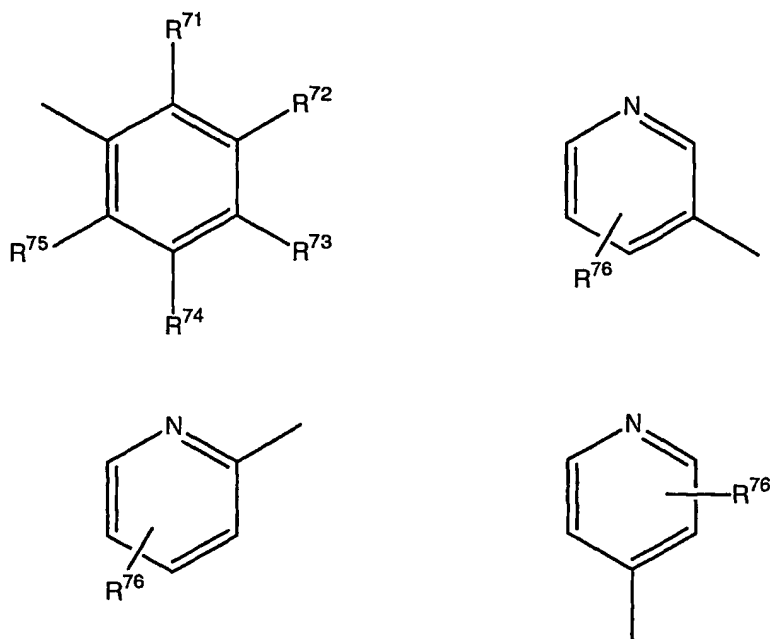
wherein:

$X^8$  is an oxygen atom or a sulfur atom;

$R^{64}$  and  $R^{65}$ , identical to or different from each other, are independently a  
 5 hydrogen atom, a halogen atom, a  $C_1 - C_6$  lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a nitro group, a nitrile group, or a carboxyl group;

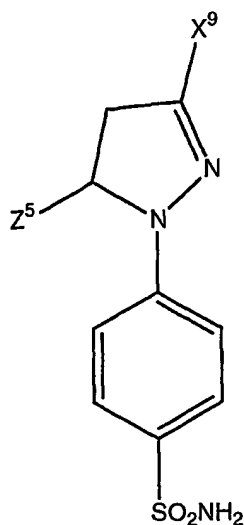
$R^{66}$  is a group of a formula:  $S(O)_n R^{68}$  wherein  $n$  is an integer of 0~2,  $R^{68}$  is  
 10 a hydrogen atom, a  $C_1 - C_6$  lower alkyl group, or a group of a formula:  $NR^{69} R^{70}$  wherein  $R^{69}$  and  $R^{70}$ , identical to or different from each other, are independently a hydrogen atom, or a  $C_1 - C_6$  lower alkyl group; and

$R^{67}$  is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a  $C_1 - C_6$  lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the  
 15 following structures:



wherein:

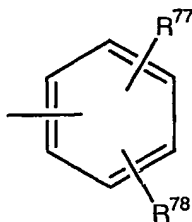
- R<sup>71</sup> through R<sup>75</sup>, identical to or different from one another, are
- 5 independently a hydrogen atom, a halogen atom, a C<sub>1</sub>–C<sub>6</sub> lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a hydroxyalkyl group, a nitro group, a group of a formula: S(O)<sub>n</sub>R<sup>68</sup>, a group of a formula: NR<sup>69</sup>R<sup>70</sup>, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,
- 10 wherein n, R<sup>68</sup>, R<sup>69</sup> and R<sup>70</sup> have the same meaning as defined by R<sup>66</sup> above; and
- R<sup>76</sup> is a hydrogen atom, a halogen atom, a C<sub>1</sub>–C<sub>6</sub> lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.
- 15 **[00092]** Materials that can serve as the Cox-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:



XV

wherein:

- 5  $X^9$  is selected from the group consisting of  $C_1 - C_6$  trihalomethyl, preferably trifluoromethyl;  $C_1 - C_6$  alkyl; and an optionally substituted or di-substituted phenyl group of formula XVI:



XVI

10

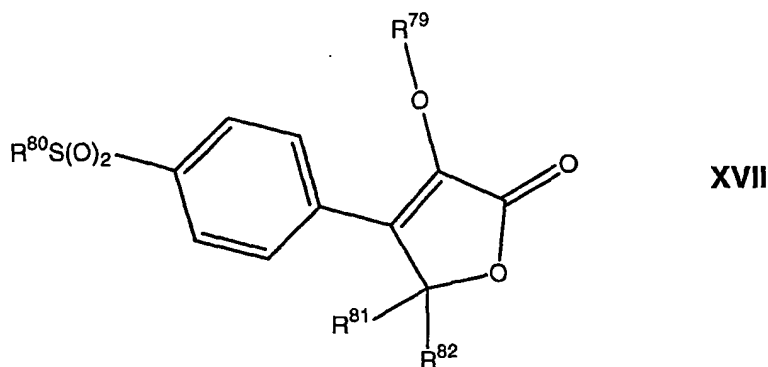
wherein:

- $R^{77}$  and  $R^{78}$  are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro;  $C_1 - C_6$  alkyl, preferably  $C_1 - C_3$  alkyl;  $C_1 - C_6$  alkoxy, preferably  $C_1 - C_3$  alkoxy; carboxy;  $C_1 - C_6$  trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;
- 15

$Z^5$  is selected from the group consisting of substituted and unsubstituted aryl.

[00093] Compounds useful as Cox-2 selective inhibitors of the present invention include heterocycles that are described in U.S. Patent No.

5 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



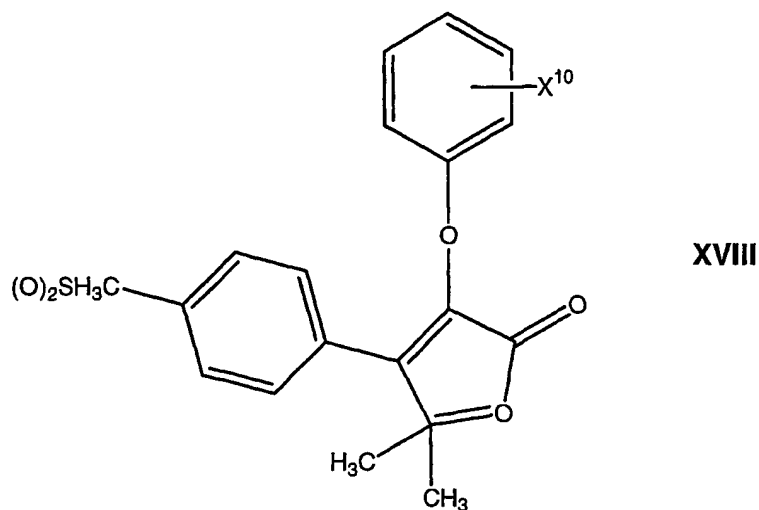
wherein:

10  $R^{79}$  is a mono-, di-, or tri-substituted  $C_1 - C_{12}$  alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched  $C_2 - C_{10}$  alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched  $C_2 - C_{10}$  alkynyl, or an unsubstituted or mono-, di- or tri-substituted  $C_3 - C_{12}$  cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted  $C_5 - C_{12}$  cycloalkynyl, wherein the substituents are chosen from the group consisting of halo selected from F, Cl, Br, and I, OH,  $CF_3$ ,  $C_3 - C_6$  cycloalkyl, =O, dioxolane, CN;

$R^{80}$  is selected from the group consisting of  $CH_3$ ,  $NH_2$ ,  $NHC(O)CF_3$ , and  $NHCH_3$ ;

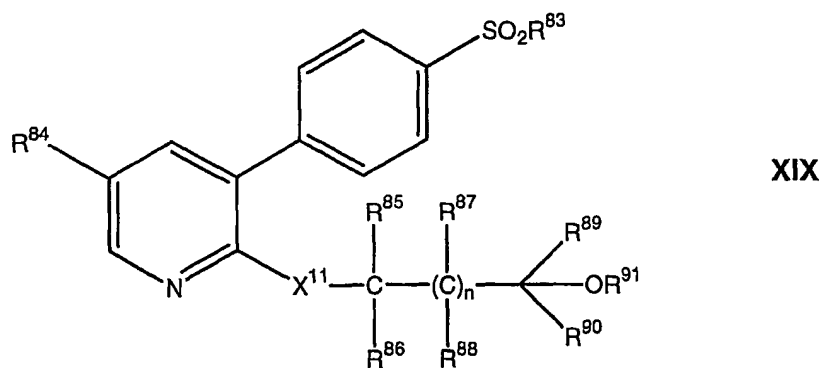
20  $R^{81}$  and  $R^{82}$  are independently chosen from the group consisting of hydrogen and  $C_1 - C_{10}$  alkyl; or  $R^{81}$  and  $R^{82}$  together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

[00094] Formula **XVIII** is:



wherein  $X^{10}$  is fluoro or chloro.

- 5 **[00095]** Materials that can serve as the Cox-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



10

or a pharmaceutically acceptable salt thereof,

wherein:

$X^{11}$  is selected from the group consisting of O, S, and a bond;



n is 0 or 1;

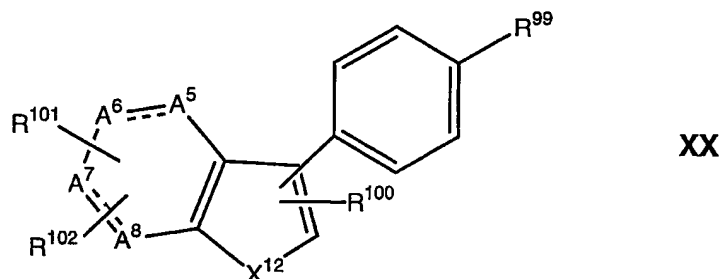
$R^{83}$  is selected from the group consisting of  $CH_3$ ,  $NH_2$ , and  $NHC(O)CF_3$ ;

$R^{84}$  is chosen from the group consisting of halo,  $C_1-C_6$  alkoxy,  $C_1-C_6$  alkylthio, CN,  $C_1-C_6$  alkyl,  $C_1-C_6$  fluoroalkyl,  $N_3$ ,  $-CO_2 R^{92}$ , hydroxyl,  $C(R^{93})(R^{94})-OH$ ,  $-C_1-C_6$  alkyl- $CO_2-R^{95}$ ,  $C_1-C_6$  fluoroalkoxy,  $NO_2$ ,  $NR^{96} R^{97}$ , and  $NHCOR^{98}$ ;

$R^{85}$  to  $R^{89}$  are independently chosen from the group consisting of hydrogen and  $C_1-C_6$  alkyl;

or  $R^{85}$  and  $R^{89}$ , or  $R^{89}$  and  $R^{90}$  together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or  $R^{85}$  and  $R^{87}$  are joined to form a bond.

[00096] Compounds that are useful as the Cox-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula XX:



and pharmaceutically acceptable salts thereof wherein:

$-A^5=A^6-A^7=A^8-$  is selected from the group consisting of:

(a)  $-CH=CH-CH=CH-$ ,

(b)  $-CH_2-CH_2-CH_2-C(O)-$ ,  $-CH_2-CH_2-C(O)-CH_2-$ ,  $-CH_2-C(O)-CH_2-CH_2-$ ,  $-C(O)-CH_2-CH_2-CH_2-$ ,

(c)  $-CH_2-CH_2-C(O)-$ ,  $-CH_2-C(O)-CH_2-$ ,  $-C(O)-CH_2-CH_2-$

(d)  $-CH_2-CH_2-O-C(O)-$ ,  $CH_2-O-C(O)-CH_2-$ ,  $-O-C(O)-CH_2-CH_2-$ ,

- (e)  $-\text{CH}_2-\text{CH}_2-\text{C}(\text{O})-\text{O}-$ ,  $-\text{CH}_2-\text{C}(\text{O})-\text{OCH}_2-$ ,  $-\text{C}(\text{O})-\text{O}-$   
 $\text{CH}_2-\text{CH}_2-$ ,  
 (f)  $-\text{C}(\text{R}^{105})_2-\text{O}-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{O}-\text{C}(\text{R}^{105})_2-$ ,  $-\text{O}-\text{C}(\text{O})-$   
 $\text{C}(\text{R}^{105})_2-$ ,  $-\text{C}(\text{R}^{105})_2-\text{C}(\text{O})-\text{O}-$ ,  
 5 (g)  $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$ ,  
 (h)  $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$ ,  
 (i)  $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$ ,  
 (j)  $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$ ,  
 (k)  $-\text{N}=\text{CH}-\text{CH}=\text{N}-$ ,  
 10 (l)  $-\text{N}=\text{CH}-\text{N}=\text{CH}-$ ,  
 (m)  $-\text{CH}=\text{N}-\text{CH}=\text{N}-$ ,  
 (n)  $-\text{S}-\text{CH}=\text{N}-$ ,  
 (o)  $-\text{S}-\text{N}=\text{CH}-$ ,  
 (p)  $-\text{N}=\text{N}-\text{NH}-$ ,  
 15 (q)  $-\text{CH}=\text{N}-\text{S}-$ , and  
 (r)  $-\text{N}=\text{CH}-\text{S}-$ ;  
 $\text{R}^{99}$  is selected from the group consisting of  $\text{S}(\text{O})_2\text{CH}_3$ ,  $\text{S}(\text{O})_2\text{NH}_2$ ,  
 $\text{S}(\text{O})_2\text{NHCOCF}_3$ ,  $\text{S}(\text{O})(\text{NH})\text{CH}_3$ ,  $\text{S}(\text{O})(\text{NH})\text{NH}_2$ ,  $\text{S}(\text{O})(\text{NH})\text{NHCOCF}_3$ ,  
 $\text{P}(\text{O})(\text{CH}_3)\text{OH}$ , and  $\text{P}(\text{O})(\text{CH}_3)\text{NH}_2$ ;  
 20  $\text{R}^{100}$  is selected from the group consisting of:  
 (a)  $\text{C}_1-\text{C}_6$  alkyl,  
 (b)  $\text{C}_3-\text{C}_7$  cycloalkyl,  
 (c) mono- or di-substituted phenyl or naphthyl wherein the substituent is  
 selected from the group consisting of:  
 25 (1) hydrogen,  
 (2) halo, including F, Cl, Br, I,  
 (3)  $\text{C}_1-\text{C}_6$  alkoxy,  
 (4)  $\text{C}_1-\text{C}_6$  alkylthio,  
 (5) CN,  
 30 (6)  $\text{CF}_3$ ,  
 (7)  $\text{C}_1-\text{C}_6$  alkyl,  
 (8)  $\text{N}_3$ ,

- (9)  $-\text{CO}_2 \text{H}$ ,
- (10)  $-\text{CO}_2 -\text{C}_1 -\text{C}_4 \text{ alkyl}$ ,
- (11)  $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{OH}$ ,
- (12)  $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{O}-\text{C}_1 -\text{C}_4 \text{ alkyl}$ , and
- 5 (13)  $-\text{C}_1 -\text{C}_6 \text{ alkyl}-\text{CO}_2 -\text{R}^{106}$ ;

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

- (1) hydrogen,
- (2) halo, including fluoro, chloro, bromo and iodo,
- (3)  $\text{C}_1 -\text{C}_6 \text{ alkyl}$ ,
- 15 (4)  $\text{C}_1 -\text{C}_6 \text{ alkoxy}$ ,
- (5)  $\text{C}_1 -\text{C}_6 \text{ alkylthio}$ ,
- (6) CN,
- (7)  $\text{CF}_3$ ,
- (8)  $\text{N}_3$ ,
- 20 (9)  $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{OH}$ , and
- (10)  $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{O}-\text{C}_1 -\text{C}_4 \text{ alkyl}$ ;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);  $\text{R}^{101}$  and  $\text{R}^{102}$  are the substituents residing on any position of  $-\text{A}^5=\text{A}^6-\text{A}^7=\text{A}^8-$  and are selected independently from the group consisting of:

- 25 (a) hydrogen,
- (b)  $\text{CF}_3$ ,
- (c) CN,
- (d)  $\text{C}_1 -\text{C}_6 \text{ alkyl}$ ,
- (e)  $-\text{Q}^3$  wherein  $\text{Q}^3$  is  $\text{Q}^4$ ,  $\text{CO}_2 \text{H}$ ,  $\text{C}(\text{R}^{103})(\text{R}^{104})\text{OH}$ ,
- 30 (f)  $-\text{O}-\text{Q}^4$ ,
- (g)  $-\text{S}-\text{Q}^4$ , and
- (h) optionally substituted:

- (1)  $-\text{C}_1-\text{C}_5$  alkyl- $\text{Q}^3$ ,  
 (2)  $-\text{O}-\text{C}_1-\text{C}_5$  alkyl- $\text{Q}^3$ ,  
 (3)  $-\text{S}-\text{C}_1-\text{C}_5$  alkyl- $\text{Q}^3$ ,  
 (4)  $-\text{C}_1-\text{C}_3$  alkyl- $\text{O}-\text{C}_{1-3}$  alkyl- $\text{Q}^3$ ,  
 (5)  $-\text{C}_1-\text{C}_3$  alkyl- $\text{S}-\text{C}_{1-3}$  alkyl- $\text{Q}^3$ ,  
 (6)  $-\text{C}_1-\text{C}_5$  alkyl- $\text{O}-\text{Q}^4$ ,  
 (7)  $-\text{C}_1-\text{C}_5$  alkyl- $\text{S}-\text{Q}^4$ ,

wherein the substituent resides on the alkyl chain and the substituent is  $\text{C}_1-\text{C}_3$  alkyl, and  $\text{Q}^3$  is  $\text{Q}^4$ ,  $\text{CO}_2\text{H}$ ,  $\text{C}(\text{R}^{103})(\text{R}^{104})\text{OH}$   $\text{Q}^4$  is  $\text{CO}_2-\text{C}_1-\text{C}_4$  alkyl, tetrazolyl-5-yl, or  $\text{C}(\text{R}^{103})(\text{R}^{104})\text{O}-\text{C}_1-\text{C}_4$  alkyl;

$\text{R}^{103}$ ,  $\text{R}^{104}$  and  $\text{R}^{105}$  are each independently selected from the group consisting of hydrogen and  $\text{C}_1-\text{C}_6$  alkyl; or

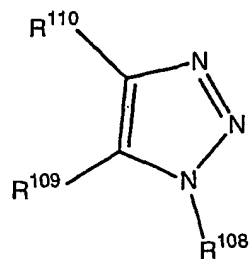
$\text{R}^{103}$  and  $\text{R}^{104}$  together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two  $\text{R}^{105}$  groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

$\text{R}^{106}$  is hydrogen or  $\text{C}_1-\text{C}_6$  alkyl;

$\text{R}^{107}$  is hydrogen,  $\text{C}_1-\text{C}_6$  alkyl or aryl;

$\text{X}^7$  is O, S,  $\text{NR}^{107}$ , CO,  $\text{C}(\text{R}^{107})_2$ ,  $\text{C}(\text{R}^{107})(\text{OH})$ ,  $-\text{C}(\text{R}^{107})=\text{C}(\text{R}^{107})-$ ;  $-\text{C}(\text{R}^{107})=\text{N}-$ ; or  $-\text{N}=\text{C}(\text{R}^{107})-$ .

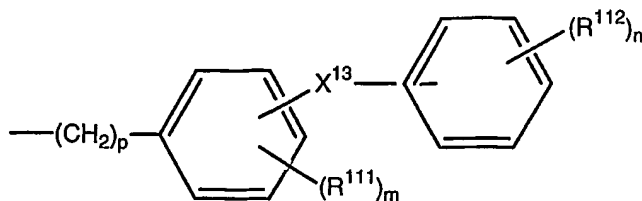
**[00097]** Compounds that may act as Cox-2 selective inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



**XXI**

wherein:

$R^{108}$  is:



5 wherein:

$p$  is 0 to 2;  $m$  is 0 to 4; and  $n$  is 0 to 5;

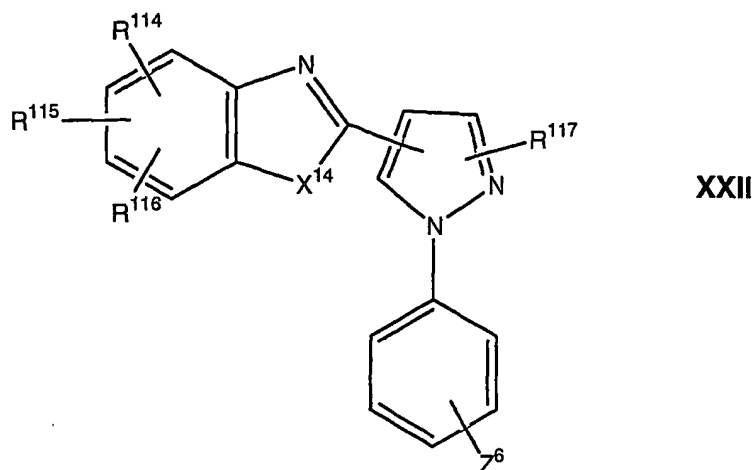
$X^{13}$  is O, S, SO,  $SO_2$ , CO, CHCN,  $CH_2$  or  $C=NR^{113}$  where  $R^{113}$  is hydrogen, loweralkyl, hydroxyl, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano;

10  $R^{111}$  and  $R^{112}$  are independently halogen, cyano, trifluoromethyl, loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifluoromethoxy, acetamido, loweralkylthio, loweralkylsulfanyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfanyl, or trifluoromethylsulfonyl;

15  $R^{109}$  is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, or guanidino; and

$R^{110}$  is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

20 **[00098]** Pyrazole derivatives such as those described in U.S. Patent 6,136,831 can serve as a Cox-2 selective inhibitor of the present invention. Such pyrazole derivatives have the formula shown below in formula XXII:



wherein:

$R^{114}$  is hydrogen or halogen;

$R^{115}$  and  $R^{116}$  are each independently hydrogen, halogen, lower alkyl,  
5 lower alkoxy, hydroxyl or lower alkanoyloxy;

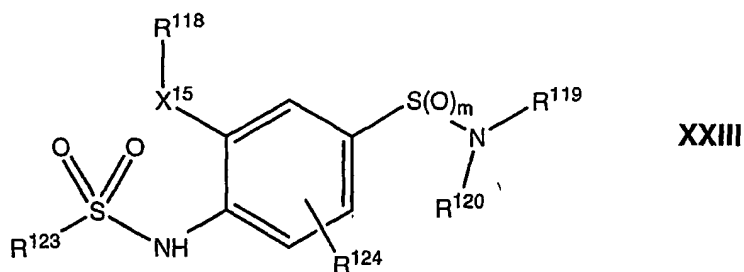
$R^{117}$  is lower haloalkyl or lower alkyl;

$X^{14}$  is sulfur, oxygen or NH; and

$Z^6$  is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

10 **[00099]** Materials that can serve as a Cox-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



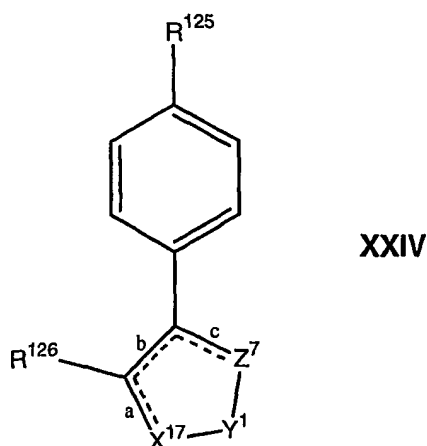
15 wherein:

$X^{15}$  denotes oxygen, sulphur or NH;

- $R^{118}$  is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl,  $CF_3$ , cyano or alkoxy;
- $R^{119}$  and  $R^{120}$ , independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group  $(CH_2)_n - X^{16}$ ; or
- $R^{119}$  and  $R^{120}$ , together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group  $(CH_2)_n - X^{16}$ ;
- $X^{16}$  denotes halogen,  $NO_2$ ,  $-OR^{121}$ ,  $-COR^{121}$ ,  $-CO_2 R^{121}$ ,  $-OCO_2 R^{121}$ ,  $-CN$ ,  $-CONR^{121} OR^{122}$ ,  $-CONR^{121} R^{122}$ ,  $-SR^{121}$ ,  $-S(O)R^{121}$ ,  $-S(O)_2 R^{121}$ ,  $-NR^{121} R^{122}$ ,  $-NHC(O)R^{121}$ ,  $-NHS(O)_2 R^{121}$ ;
- $n$  denotes a whole number from 0 to 6;
- $R^{123}$  denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;
- $R^{124}$  denotes halogen, hydroxyl, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen,  $NO_2$ ,  $-OR^{121}$ ,  $-COR^{121}$ ,  $-CO_2 R^{121}$ ,  $-OCO_2 R^{121}$ ,  $-CN$ ,  $-CONR^{121} OR^{122}$ ,  $-CONR^{121} R^{122}$ ,  $-SR^{121}$ ,  $-S(O)R^{121}$ ,  $-S(O)_2 R^{121}$ ,  $-NR^{121} R^{122}$ ,  $-NHC(O)R^{121}$ ,  $-NHS(O)_2 R^{121}$ , or a polyfluoroalkyl group;
- $R^{121}$  and  $R^{122}$ , independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and
- $m$  denotes a whole number from 0 to 2;
- and the pharmaceutically-acceptable salts thereof.

**[000100]** Compounds that are useful as Cox-2 selective inhibitors of the present invention include phenyl heterocycles that are described in U.S.

Patent Nos. 5,474,995 and 6,239,173. Such phenyl heterocyclic compounds have the formula shown below in formula XXIV:



or pharmaceutically acceptable salts thereof wherein:

5  $X^{17}-Y^1-Z^7$ -is selected from the group consisting of:

- (a)  $-\text{CH}_2 \text{CH}_2 \text{CH}_2 -$ ,
- (b)  $-\text{C}(\text{O})\text{CH}_2 \text{CH}_2 -$ ,
- (c)  $-\text{CH}_2 \text{CH}_2 \text{C}(\text{O})-$ ,
- (d)  $-\text{CR}^{129} (\text{R}^{129'})-\text{O}-\text{C}(\text{O})-$ ,
- 10 (e)  $-\text{C}(\text{O})-\text{O}-\text{CR}^{129} (\text{R}^{129'})-$ ,
- (f)  $-\text{CH}_2 -\text{NR}^{127} -\text{CH}_2 -$ ,
- (g)  $-\text{CR}^{129} (\text{R}^{129'})-\text{NR}^{127} -\text{C}(\text{O})-$ ,
- (h)  $-\text{CR}^{128}=\text{CR}^{128'}-\text{S}-$ ,
- (i)  $-\text{S}-\text{CR}^{128}=\text{CR}^{128'}-$ ,
- 15 (j)  $-\text{S}-\text{N}=\text{CH}-$ ,
- (k)  $-\text{CH}=\text{N}-\text{S}-$ ,
- (l)  $-\text{N}=\text{CR}^{128} -\text{O}-$ ,
- (m)  $-\text{O}-\text{CR}^{128}=\text{N}-$ ,
- (n)  $-\text{N}=\text{CR}^{128} -\text{NH}-$ ,
- 20 (o)  $-\text{N}=\text{CR}^{128} -\text{S}-$ , and
- (p)  $-\text{S}-\text{CR}^{128}=\text{N}-$ ,
- (q)  $-\text{C}(\text{O})-\text{NR}^{127} -\text{CR}^{129} (\text{R}^{129'})-$ ,



(r)  $-\text{R}^{127} \text{N}-\text{CH}=\text{CH}-$  provided  $\text{R}^{122}$  is not  $-\text{S}(\text{O})_2\text{CH}_3$ ,

(s)  $-\text{CH}=\text{CH}-\text{NR}^{127}-$  provided  $\text{R}^{125}$  is not  $-\text{S}(\text{O})_2\text{CH}_3$ ;

when side b is a double bond, and sides a and c are single bonds; and

$\text{X}^{17}-\text{Y}^1-\text{Z}^7$ -is selected from the group consisting of:

5 (a)  $=\text{CH}-\text{O}-\text{CH}=$ , and

(b)  $=\text{CH}-\text{NR}^{127}-\text{CH}=$ ,

(c)  $=\text{N}-\text{S}-\text{CH}=$ ,

(d)  $=\text{CH}-\text{S}-\text{N}=$ ,

(e)  $=\text{N}-\text{O}-\text{CH}=$ ,

10 (f)  $=\text{CH}-\text{O}-\text{N}=$ ,

(g)  $=\text{N}-\text{S}-\text{N}=$ ,

(h)  $=\text{N}-\text{O}-\text{N}=$ ,

when sides a and c are double bonds and side b is a single bond;

$\text{R}^{125}$  is selected from the group consisting of:

15 (a)  $\text{S}(\text{O})_2 \text{CH}_3$ ,

(b)  $\text{S}(\text{O})_2 \text{NH}_2$ ,

(c)  $\text{S}(\text{O})_2 \text{NHC}(\text{O})\text{CF}_3$ ,

(d)  $\text{S}(\text{O})(\text{NH})\text{CH}_3$ ,

(e)  $\text{S}(\text{O})(\text{NH})\text{NH}_2$ ,

20 (f)  $\text{S}(\text{O})(\text{NH})\text{NHC}(\text{O})\text{CF}_3$ ,

(g)  $\text{P}(\text{O})(\text{CH}_3)\text{OH}$ , and

(h)  $\text{P}(\text{O})(\text{CH}_3)\text{NH}_2$ ;

$\text{R}^{126}$  is selected from the group consisting of

(a)  $\text{C}_1-\text{C}_6$  alkyl,

25 (b)  $\text{C}_3$ ,  $\text{C}_4$ ,  $\text{C}_5$ ,  $\text{C}_6$ , and  $\text{C}_7$ , cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituent

is selected from the group consisting of:

(1) hydrogen,

(2) halo,

30 (3)  $\text{C}_1-\text{C}_6$  alkoxy,

(4)  $\text{C}_1-\text{C}_6$  alkylthio,

(5) CN,

- (6)  $\text{CF}_3$ ,  
 (7)  $\text{C}_1 - \text{C}_6$  alkyl,  
 (8)  $\text{N}_3$ ,  
 (9)  $-\text{CO}_2 \text{H}$ ,  
 5 (10)  $-\text{CO}_2 - \text{C}_1 - \text{C}_4$  alkyl,  
 (11)  $-\text{C}(\text{R}^{129})(\text{R}^{130})-\text{OH}$ ,  
 (12)  $-\text{C}(\text{R}^{129})(\text{R}^{130})-\text{O}-\text{C}_1 - \text{C}_4$  alkyl, and  
 (13)  $-\text{C}_1 - \text{C}_6$  alkyl- $\text{CO}_2 - \text{R}^{129}$  ;
- (d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a  
 10 monocyclic aromatic ring of 5 atoms, said ring having one hetero atom  
 which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the  
 heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero  
 atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said  
 substituents are selected from the group consisting of:
- 15 (1) hydrogen,  
 (2) halo, including fluoro, chloro, bromo and iodo,  
 (3)  $\text{C}_1 - \text{C}_6$  alkyl,  
 (4)  $\text{C}_1 - \text{C}_6$  alkoxy,  
 (5)  $\text{C}_1 - \text{C}_6$  alkylthio,  
 20 (6)  $\text{CN}$ ,  
 (7)  $\text{CF}_3$ ,  
 (8)  $\text{N}_3$ ,  
 (9)  $-\text{C}(\text{R}^{129})(\text{R}^{130})-\text{OH}$ , and  
 (10)  $-\text{C}(\text{R}^{129})(\text{R}^{130})-\text{O}-\text{C}_1 - \text{C}_4$  alkyl;
- 25 (e) benzoheteroaryl which includes the benzo fused analogs of (d);  
 $\text{R}^{127}$  is selected from the group consisting of:
- (a) hydrogen,  
 (b)  $\text{CF}_3$ ,  
 (c)  $\text{CN}$ ,  
 30 (d)  $\text{C}_1 - \text{C}_6$  alkyl,  
 (e) hydroxyl  $\text{C}_1 - \text{C}_6$  alkyl,  
 (f)  $-\text{C}(\text{O})- \text{C}_1 - \text{C}_6$  alkyl,

(g) optionally substituted:

- (1)  $-\text{C}_1-\text{C}_5$  alkyl- $\text{Q}^5$ ,
- (2)  $-\text{C}_1-\text{C}_5$  alkyl-O- $\text{C}_1-\text{C}_3$  alkyl- $\text{Q}^5$ ,
- (3)  $-\text{C}_1-\text{C}_3$  alkyl-S- $\text{C}_1-\text{C}_3$  alkyl- $\text{Q}^5$ ,
- 5 (4)  $-\text{C}_1-\text{C}_5$  alkyl-O- $\text{Q}^5$ , or
- (5)  $-\text{C}_1-\text{C}_5$  alkyl-S- $\text{Q}^5$ ,

wherein the substituent resides on the alkyl and the substituent is  $\text{C}_1-\text{C}_3$  alkyl;

(h)  $-\text{Q}^5$ ;

10  $\text{R}^{128}$  and  $\text{R}^{128'}$  are each independently selected from the group consisting of:

(a) hydrogen,

(b)  $\text{CF}_3$ ,

(c) CN,

15 (d)  $\text{C}_1-\text{C}_6$  alkyl,

(e)  $-\text{Q}^5$ ,

(f)  $-\text{O}-\text{Q}^5$ ;

(g)  $-\text{S}-\text{Q}^5$ , and

(h) optionally substituted:

- 20 (1)  $-\text{C}_1-\text{C}_5$  alkyl- $\text{Q}^5$ ,
- (2)  $-\text{O}-\text{C}_1-\text{C}_5$  alkyl- $\text{Q}^5$ ,
- (3)  $-\text{S}-\text{C}_1-\text{C}_5$  alkyl- $\text{Q}^5$ ,
- (4)  $-\text{C}_1-\text{C}_3$  alkyl-O- $\text{C}_1-\text{C}_3$  alkyl- $\text{Q}^5$ ,
- (5)  $-\text{C}_1-\text{C}_3$  alkyl-S- $\text{C}_1-\text{C}_3$  alkyl- $\text{Q}^5$ ,
- 25 (6)  $-\text{C}_1-\text{C}_5$  alkyl-O- $\text{Q}^5$ ,
- (7)  $-\text{C}_1-\text{C}_5$  alkyl-S- $\text{Q}^5$ ,

wherein the substituent resides on the alkyl and the substituent is  $\text{C}_1-\text{C}_3$  alkyl, and

$\text{R}^{129}$ ,  $\text{R}^{129'}$ ,  $\text{R}^{130}$ ,  $\text{R}^{131}$  and  $\text{R}^{132}$  are each independently selected from the group consisting of:

30 (a) hydrogen,

(b)  $\text{C}_1-\text{C}_6$  alkyl;

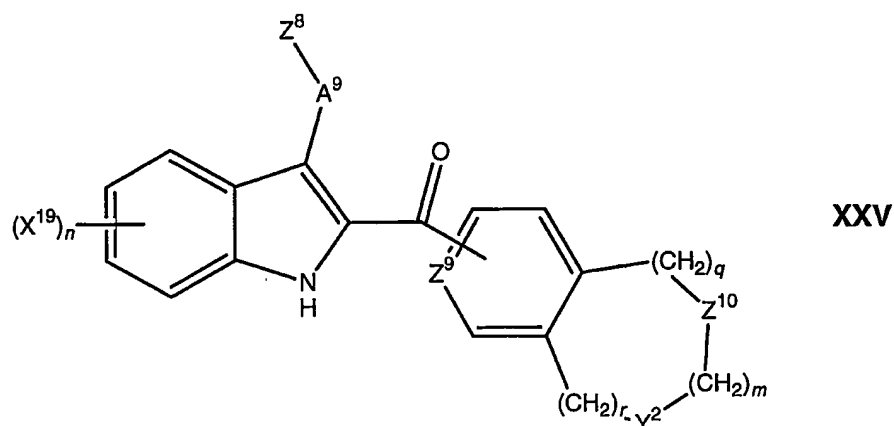
or  $R^{129}$  and  $R^{130}$  or  $R^{131}$  and  $R^{132}$  together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

$Q^5$  is  $CO_2 H$ ,  $CO_2 -C_1 -C_4$  alkyl, tetrazolyl-5-yl,  $C(R^{131})(R^{132})(OH)$ , or  $C(R^{131})(R^{132})(O-C_1 -C_4$  alkyl);

provided that when  $X-Y-Z$  is  $-S-CR^{128}=CR^{128'}$ , then  $R^{128}$  and  $R^{128'}$  are other than  $CF_3$ .

**[000101]** An exemplary phenyl heterocycle that is disclosed in U.S. Patent No. 6,239,173 is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(2H)-furanone.

**[000102]** Bicycliccarbonyl indole compounds such as those described in U.S. Patent No. 6,303,628 are useful as Cox-2 selective inhibitors of the present invention. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



or the pharmaceutically acceptable salts thereof wherein:

$A^9$  is  $C_1 -C_6$  alkylene or  $-NR^{133}-$ ;

$Z^8$  is  $C(=L^3)R^{134}$ , or  $SO_2 R^{135}$ ;

$Z^9$  is CH or N;

$Z^{10}$  and  $Y^2$  are independently selected from  $-CH_2-$ , O, S and  $-N-R^{133}$ ;

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

$X^{18}$  is independently selected from halogen,  $C_1-C_4$  alkyl, halo-substituted  $C_1-C_4$  alkyl, hydroxyl,  $C_1-C_4$  alkoxy, halo-substituted  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkylthio, nitro, amino, mono- or di- $(C_1-C_4$  alkyl)amino and cyano;

5 n is 0, 1, 2, 3 or 4;

$L^3$  is oxygen or sulfur;

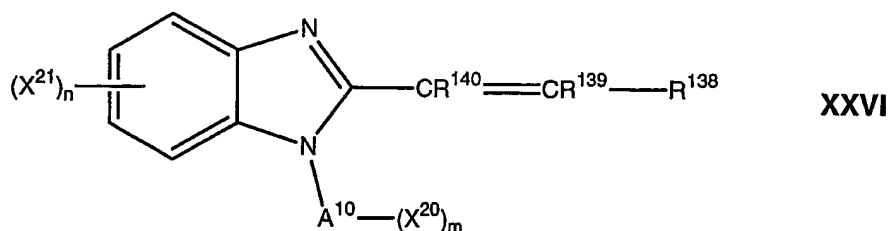
$R^{133}$  is hydrogen or  $C_1-C_4$  alkyl;

$R^{134}$  is hydroxyl,  $C_1-C_6$  alkyl, halo-substituted  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy, halo-substituted  $C_1-C_6$  alkoxy,  $C_3-C_7$  cycloalkoxy,  $C_1-C_4$  alkyl( $C_3-C_7$  cycloalkoxy),  $-NR^{136}R^{137}$ ,  $C_1-C_4$  alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen,  $C_1-C_4$  alkyl, hydroxyl,  $C_1-C_4$  alkoxy and nitro;

10  $R^{135}$  is  $C_1-C_6$  alkyl or halo-substituted  $C_1-C_6$  alkyl; and

15  $R^{136}$  and  $R^{137}$  are independently selected from hydrogen,  $C_{1-6}$  alkyl and halo-substituted  $C_1-C_6$  alkyl.

[000103] Materials that can serve as a Cox-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula XXVI:



or a pharmaceutically acceptable salt thereof, wherein:

$A^{10}$  is heteroaryl selected from

25 a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or

a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

- 5  $X^{20}$  is independently selected from halo,  $C_1 - C_4$  alkyl, hydroxyl,  $C_1 - C_4$  alkoxy, halo-substituted  $C_1 - C_4$  alkyl, hydroxyl-substituted  $C_1 - C_4$  alkyl, ( $C_1 - C_4$  alkoxy) $C_1 - C_4$  alkyl, halo-substituted  $C_1 - C_4$  alkoxy, amino, N-( $C_1 - C_4$  alkyl)amino, N, N-di( $C_1 - C_4$  alkyl)amino, [N-( $C_1 - C_4$  alkyl)amino] $C_1 - C_4$  alkyl, [N, N-di( $C_1 - C_4$  alkyl)amino] $C_1 - C_4$  alkyl, N-( $C_1 - C_4$  alkanoyl)amino, N-( $C_1 - C_4$  alkyl)( $C_1 - C_4$  alkanoyl)amino, N-[( $C_1 - C_4$  alkyl)sulfonyl]amino, N-[(halo-substituted  $C_1 - C_4$  alkyl)sulfonyl]amino,  $C_1 - C_4$  alkanoyl, carboxy, ( $C_1 - C_4$  alkoxy)carbonyl, carbamoyl, [N-( $C_1 - C_4$  alkyl)amino]carbonyl, [N, N-di( $C_1 - C_4$  alkyl)amino]carbonyl, cyano, nitro, mercapto, ( $C_1 - C_4$  alkyl)thio, ( $C_1 - C_4$  alkyl)sulfinyl, ( $C_1 - C_4$  alkyl)sulfonyl, aminosulfonyl, [N-( $C_1 - C_4$  alkyl)amino]sulfonyl and [N, N-di( $C_1 - C_4$  alkyl)amino]sulfonyl;
- 10  $X^{21}$  is independently selected from halo,  $C_1 - C_4$  alkyl, hydroxyl,  $C_1 - C_4$  alkoxy, halo-substituted  $C_1 - C_4$  alkyl, hydroxyl-substituted  $C_1 - C_4$  alkyl, ( $C_1 - C_4$  alkoxy) $C_1 - C_4$  alkyl, halo-substituted  $C_1 - C_4$  alkoxy, amino, N-( $C_1 - C_4$  alkyl)amino, N, N-di( $C_1 - C_4$  alkyl)amino, [N-( $C_1 - C_4$  alkyl)amino] $C_1 - C_4$  alkyl, [N, N-di( $C_1 - C_4$  alkyl)amino] $C_1 - C_4$  alkyl, N-( $C_1 - C_4$  alkanoyl)amino, N-( $C_1 - C_4$  alkyl)-N-( $C_1 - C_4$  alkanoyl) amino, N-[( $C_1 - C_4$  alkyl)sulfonyl]amino, N-[(halo-substituted  $C_1 - C_4$  alkyl)sulfonyl]amino,  $C_1 - C_4$  alkanoyl, carboxy, ( $C_1 - C_4$  alkoxy)hydroxyl, carbamoyl, [N-( $C_1 - C_4$  alkyl)amino]carbonyl, [N, N-di( $C_1 - C_4$  alkyl)amino]carbonyl, N-carbamoylamino, cyano, nitro, mercapto, ( $C_1 - C_4$  alkyl)thio, ( $C_1 - C_4$  alkyl)sulfinyl, ( $C_1 - C_4$  alkyl)sulfonyl, aminosulfonyl, [N-( $C_1 - C_4$  alkyl)amino]sulfonyl and [N, N-di( $C_1 - C_4$  alkyl)amino]sulfonyl;
- 15  $R^{138}$  is selected from:
- hydrogen;
- 20 straight or branched  $C_1 - C_4$  alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from

- halo, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, amino, N-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino and N, N-di(C<sub>1</sub>–C<sub>4</sub> alkyl)amino;
- C<sub>3</sub>–C<sub>8</sub> cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, amino, N-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino and N, N-di(C<sub>1</sub>–C<sub>4</sub> alkyl)amino;
- C<sub>4</sub>–C<sub>8</sub> cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, amino, N-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino and N, N-di(C<sub>1</sub>–C<sub>4</sub> alkyl)amino;
- phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, halo-substituted C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl-substituted C<sub>1</sub>–C<sub>4</sub> alkyl, (C<sub>1</sub>–C<sub>4</sub> alkoxy)C<sub>1</sub>–C<sub>4</sub> alkyl, halo-substituted C<sub>1</sub>–C<sub>4</sub> alkoxy, amino, N-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, N, N-di(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, [N-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino]C<sub>1</sub>–C<sub>4</sub> alkyl, [N, N-di(C<sub>1</sub>–C<sub>4</sub> alkyl)amino]C<sub>1</sub>–C<sub>4</sub> alkyl, N-(C<sub>1</sub>–C<sub>4</sub> alkanoyl)amino, N-[C<sub>1</sub>–C<sub>4</sub> alkyl](C<sub>1</sub>–C<sub>4</sub> alkanoyl)amino, N-[(C<sub>1</sub>–C<sub>4</sub> alkyl)sulfonyl]amino, N-[(halo-substituted C<sub>1</sub>–C<sub>4</sub> alkyl)sulfonyl]amino, C<sub>1</sub>–C<sub>4</sub> alkanoyl, carboxy, (C<sub>1</sub>–C<sub>4</sub> alkoxy)carbonyl, carbomoyl, [N-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino]carbonyl, [N, N-di(C<sub>1</sub>–C<sub>4</sub> alkyl)amino]carbonyl, cyano, nitro, mercapto, (C<sub>1</sub>–C<sub>4</sub> alkyl)thio, (C<sub>1</sub>–C<sub>4</sub> alkyl)sulfinyl, (C<sub>1</sub>–C<sub>4</sub> alkyl)sulfonyl, aminosulfonyl, [N-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino]sulfonyl and [N, N-di(C<sub>1</sub>–C<sub>4</sub> alkyl)amino]sulfonyl; and
- heteroaryl selected from:
- a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and
- said heteroaryl being optionally substituted with one to three substituent(s) selected from X<sup>20</sup>;
- R<sup>139</sup> and R<sup>140</sup> are independently selected from:

hydrogen;

halo;

C<sub>1</sub>–C<sub>4</sub> alkyl;

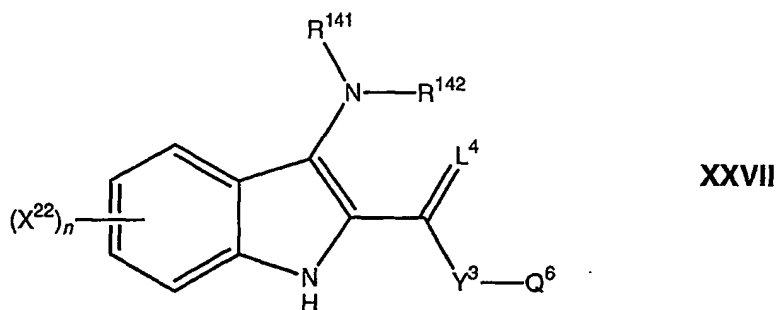
phenyl optionally substituted with one to three substituent(s) wherein said  
 5 substituents are independently selected from halo, C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl,  
 C<sub>1</sub>–C<sub>4</sub> alkoxy, amino, N-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino and N, N-di(C<sub>1</sub>–C<sub>4</sub>  
 alkyl)amino;

or R<sup>138</sup> and R<sup>139</sup> can form, together with the carbon atom to which they are  
 attached, a C<sub>3</sub>–C<sub>7</sub> cycloalkyl ring;

10 m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

**[000104]** Compounds that may be employed as a Cox-2 selective  
 inhibitor of the present invention include indole compounds that are  
 described in U.S. Patent No. 6,300,363. Such indole compounds have  
 15 the formula shown below in formula **XXVII**:



and the pharmaceutically acceptable salts thereof, wherein:

L<sup>4</sup> is oxygen or sulfur;

Y<sup>3</sup> is a direct bond or C<sub>1</sub>–C<sub>4</sub> alkylidene;

20 Q<sup>6</sup> is:

(a) C<sub>1</sub>–C<sub>6</sub> alkyl or halosubstituted C<sub>1</sub>–C<sub>6</sub> alkyl, said alkyl being optionally  
 substituted with up to three substituents independently selected from  
 hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, amino and mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino,

(b) C<sub>3</sub>–C<sub>7</sub> cycloalkyl optionally substituted with up to three substituents

25 independently selected from hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkyl and C<sub>1</sub>–C<sub>4</sub> alkoxy,



(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C<sub>1</sub>–C<sub>4</sub> alkyl, halosubstituted C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, halosubstituted C<sub>1</sub>–C<sub>4</sub> alkoxy, S(O)<sub>m</sub> R<sup>143</sup>, SO<sub>2</sub> NH<sub>2</sub>, SO<sub>2</sub> N(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>, amino, mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, NHSO<sub>2</sub> R<sup>143</sup>, NHC(O)R<sup>143</sup>, CN, CO<sub>2</sub> H, CO<sub>2</sub> (C<sub>1</sub>–C<sub>4</sub> alkyl), C<sub>1</sub>–C<sub>4</sub> alkyl-OH, C<sub>1</sub>–C<sub>4</sub> alkyl-OR<sup>143</sup>, CONH<sub>2</sub>, CONH(C<sub>1</sub>–C<sub>4</sub> alkyl), CON(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub> and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C<sub>1</sub>–C<sub>4</sub> alkyl, CF<sub>3</sub>, hydroxyl, OR<sup>143</sup>, S(O)<sub>m</sub> R<sup>143</sup>, amino, mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from:

(d-1) halo, C<sub>1</sub>–C<sub>4</sub> alkyl, halosubstituted C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, halosubstituted C<sub>1</sub>–C<sub>4</sub> alkoxy, C<sub>1</sub>–C<sub>4</sub> alkyl-OH, S(O)<sub>m</sub> R<sup>143</sup>, SO<sub>2</sub> NH<sub>2</sub>, SO<sub>2</sub> N(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>, amino, mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, NHSO<sub>2</sub> R<sup>143</sup>, NHC(O)R<sup>143</sup>, CN, CO<sub>2</sub> H, CO<sub>2</sub> (C<sub>1</sub>–C<sub>4</sub> alkyl), C<sub>1</sub>–C<sub>4</sub> alkyl-OR<sup>143</sup>, CONH<sub>2</sub>, CONH(C<sub>1</sub>–C<sub>4</sub> alkyl), CON(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF<sub>3</sub>, C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, OCF<sub>3</sub>, SR<sup>143</sup>, SO<sub>2</sub> CH<sub>3</sub>, SO<sub>2</sub> NH<sub>2</sub>, amino, C<sub>1-4</sub> alkylamino and NHSO<sub>2</sub> R<sup>143</sup>;

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R<sup>141</sup> is hydrogen or C<sub>1</sub>–C<sub>6</sub> alkyl optionally substituted with a substituent selected independently from hydroxyl, OR<sup>143</sup>, nitro, amino, mono- or di-

C<sub>1</sub>–C<sub>4</sub> alkyl)amino, CO<sub>2</sub> H, CO<sub>2</sub> (C<sub>1</sub>–C<sub>4</sub> alkyl), CONH<sub>2</sub>, CONH(C<sub>1</sub>–C<sub>4</sub> alkyl) and CON(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>;

R<sup>142</sup> is:

(a) hydrogen,

5 (b) C<sub>1</sub>–C<sub>4</sub> alkyl,

(c) C(O)R<sup>145</sup>,

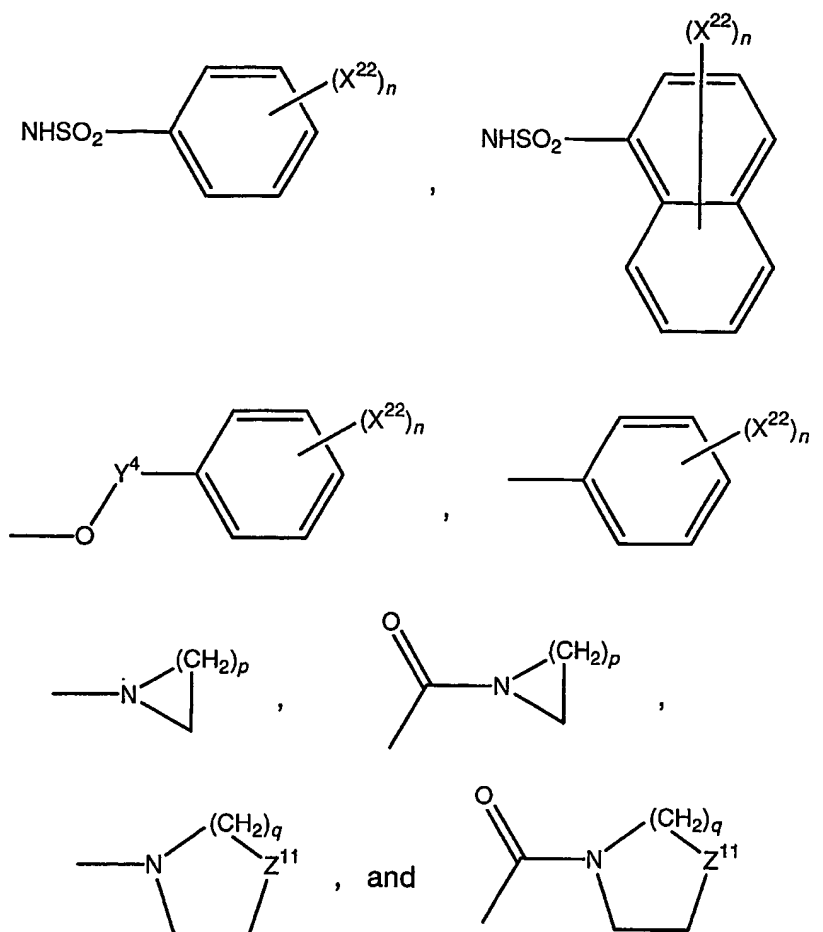
wherein R<sup>145</sup> is selected from:

(c-1) C<sub>1</sub>–C<sub>22</sub> alkyl or C<sub>2</sub>–C<sub>22</sub> alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently

10 selected from:

(c-1-1) halo, hydroxyl, OR<sup>143</sup>, S(O)<sub>m</sub> R<sup>143</sup>, nitro, amino, mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, NHSO<sub>2</sub> R<sup>143</sup>, CO<sub>2</sub> H, CO<sub>2</sub> (C<sub>1</sub>–C<sub>4</sub> alkyl), CONH<sub>2</sub>, CONH(C<sub>1</sub>–C<sub>4</sub> alkyl), CON(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>, OC(O)R<sup>143</sup>, thienyl, naphthyl and groups of the following formulas:

15



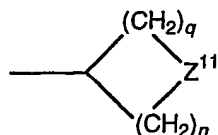
(c-2)  $\text{C}_1 - \text{C}_{22}$  alkyl or  $\text{C}_2 - \text{C}_{22}$  alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3)  $-\text{Y}^5 - \text{C}_3 - \text{C}_7$  cycloalkyl or  $-\text{Y}^5 - \text{C}_3 - \text{C}_7$  cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1)  $\text{C}_1 - \text{C}_4$  alkyl, hydroxyl,  $\text{OR}^{143}$ ,  $\text{S}(\text{O})_m \text{R}^{143}$ , amino, mono- or di- ( $\text{C}_1 - \text{C}_4$  alkyl)amino,  $\text{CONH}_2$ ,  $\text{CONH}(\text{C}_1 - \text{C}_4 \text{ alkyl})$  and  $\text{CON}(\text{C}_1 - \text{C}_4 \text{ alkyl})_2$ ,

(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

- (c-4-1) halo, C<sub>1</sub>–C<sub>8</sub> alkyl, C<sub>1</sub>–C<sub>4</sub> alkyl-OH, hydroxyl, C<sub>1</sub>–C<sub>8</sub> alkoxy, halosubstituted C<sub>1</sub>–C<sub>8</sub> alkyl, halosubstituted C<sub>1</sub>–C<sub>8</sub> alkoxy, CN, nitro, S(O)<sub>m</sub> R<sup>143</sup>, SO<sub>2</sub> NH<sub>2</sub>, SO<sub>2</sub> NH(C<sub>1</sub>–C<sub>4</sub> alkyl), SO<sub>2</sub> N(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>, amino, C<sub>1</sub>–C<sub>4</sub> alkylamino, di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, CONH<sub>2</sub>,  
 5 CONH(C<sub>1</sub>–C<sub>4</sub> alkyl), CON(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>, OC(O)R<sup>143</sup>, and phenyl optionally substituted with up to three substituents independently selected from halo, C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, OCH<sub>3</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, CN, nitro, amino, mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, CO<sub>2</sub> H, CO<sub>2</sub> (C<sub>1</sub>–C<sub>4</sub> alkyl) and CONH<sub>2</sub>,  
 10 (c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:  
 (c-5-1) halo, C<sub>1</sub>–C<sub>8</sub> alkyl, C<sub>1</sub>–C<sub>4</sub> alkyl-OH, hydroxyl, C<sub>1</sub>–C<sub>8</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, CN, nitro, S(O)<sub>m</sub> R<sup>143</sup>, amino, mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, CONH<sub>2</sub>, CONH(C<sub>1</sub>–C<sub>4</sub> alkyl), CON(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>, CO<sub>2</sub> H and CO<sub>2</sub> (C<sub>1</sub>–C<sub>4</sub> alkyl), and —Y-phenyl, said phenyl being  
 15 optionally substituted with up to three substituents independently selected halogen, C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, CN, nitro, S(O)<sub>m</sub> R<sup>143</sup>, amino, mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, CO<sub>2</sub> H, CO<sub>2</sub> (C<sub>1</sub>–C<sub>4</sub> alkyl), CONH<sub>2</sub>, CONH(C<sub>1</sub>–C<sub>4</sub> alkyl) and CON(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub>,  
 20 (c-6) a group of the following formula:



- 25 X<sup>22</sup> is halo, C<sub>1</sub>–C<sub>4</sub> alkyl, hydroxyl, C<sub>1</sub>–C<sub>4</sub> alkoxy, halosubstituted C<sub>1</sub>–C<sub>4</sub> alkoxy, S(O)<sub>m</sub> R<sup>143</sup>, amino, mono- or di-(C<sub>1</sub>–C<sub>4</sub> alkyl)amino, NHSO<sub>2</sub> R<sup>143</sup>, nitro, halosubstituted C<sub>1</sub>–C<sub>4</sub> alkyl, CN, CO<sub>2</sub> H, CO<sub>2</sub> (C<sub>1</sub>–C<sub>4</sub> alkyl), C<sub>1</sub>–C<sub>4</sub> alkyl-OH, C<sub>1</sub>–C<sub>4</sub> alkylOR<sup>143</sup>, CONH<sub>2</sub>, CONH(C<sub>1</sub>–C<sub>4</sub> alkyl) or CON(C<sub>1</sub>–C<sub>4</sub> alkyl)<sub>2</sub> ;

$R^{143}$  is  $C_1 - C_4$  alkyl or halosubstituted  $C_1 - C_4$  alkyl;

$m$  is 0, 1 or 2;  $n$  is 0, 1, 2 or 3;  $p$  is 1, 2, 3, 4 or 5;  $q$  is 2 or 3;

$Z^{11}$  is oxygen, sulfur or  $NR^{144}$ ; and

$R^{144}$  is hydrogen,  $C_1 - C_6$  alkyl, halosubstituted  $C_1 - C_4$  alkyl or  $-Y^5$ -

5 phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo,  $C_1 - C_4$  alkyl, hydroxyl,  $C_1 - C_4$  alkoxy,  $S(O)_m R^{143}$ , amino, mono- or di- $(C_1 - C_4$  alkyl)amino,  $CF_3$ ,  $OCF_3$ , CN and nitro;

with the proviso that a group of formula  $-Y^5-Q$  is not methyl or ethyl  
10 when  $X^{22}$  is hydrogen;

$L^4$  is oxygen;

$R^{141}$  is hydrogen; and

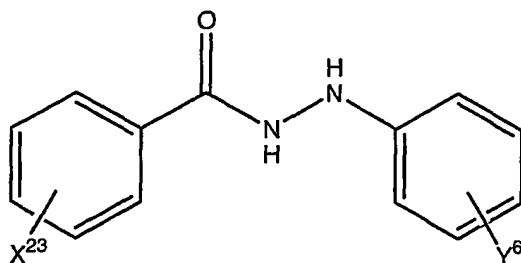
$R^{142}$  is acetyl.

[000105] Aryl phenylhydrazides that are described in U.S. Patent No.

15 6,077,869 can serve as Cox-2 selective inhibitors of the present invention.

Such aryl phenylhydrazides have the formula shown below in formula

XXVIII:

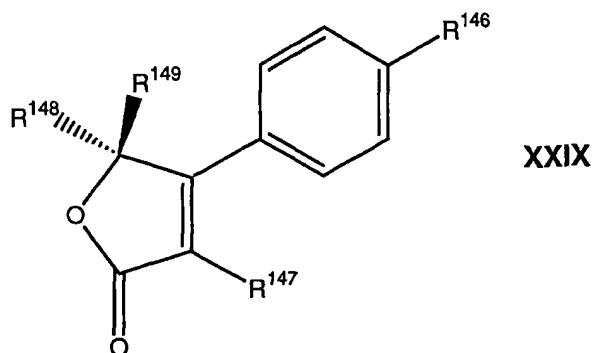


XXVIII

wherein:

20  $X^{23}$  and  $Y^6$  are selected from hydrogen, halogen, alkyl, nitro, amino, hydroxy, methoxy and methylsulfonyl; or a pharmaceutically acceptable salt thereof.

[000106] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described  
25 in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula XXIX:



or a pharmaceutical salt thereof, wherein:

$R^{146}$  is selected from the group consisting of  $\text{SCH}_3$ ,  $-\text{S}(\text{O})_2 \text{CH}_3$  and  $-\text{S}(\text{O})_2 \text{NH}_2$ ;

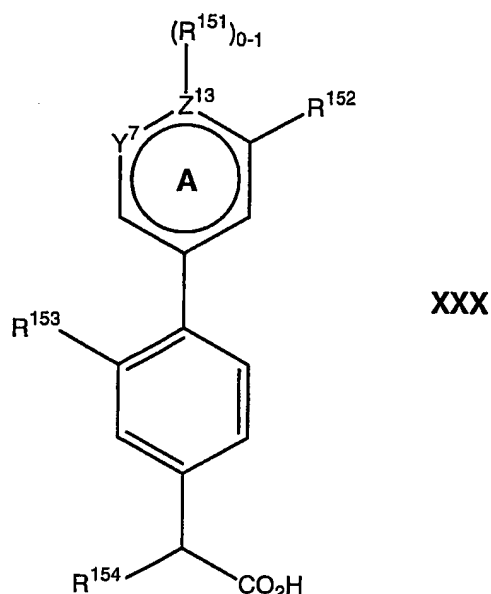
$R^{147}$  is selected from the group consisting of  $\text{OR}^{150}$ , mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

$R^{150}$  is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

$R^{148}$  is H,  $\text{C}_1 - \text{C}_4$  alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

$R^{149}$  is H,  $\text{C}_1 - \text{C}_4$  alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that  $R^{148}$  and  $R^{149}$  are not the same.

**[000107]** Materials that can serve as a Cox-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX**:



or a pharmaceutically acceptable salt, ester or tautomer thereof, wherein:

$Z^{13}$  is C or N;

when  $Z^{13}$  is N,  $R^{151}$  represents H or is absent, or is taken in conjunction  
 5 with  $R^{152}$  as described below:

when  $Z^{13}$  is C,  $R^{151}$  represents H and  $R^{152}$  is a moiety which has the  
 following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can  
 adopt an energetically stable transoid configuration and if a double bond is  
 10 present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is  
 either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to  
 within about 15 degrees;

15 or  $R^{151}$  and  $R^{152}$  are taken in combination and represent a 5- or 6-  
 membered aromatic or non-aromatic ring D fused to ring A, said ring D  
 containing 0-3 heteroatoms selected from O, S and N;  
 said ring D being lipophilic except for the atoms attached directly to ring A,  
 which are lipophilic or non-lipophilic, and said ring D having available an

energetically stable configuration planar with ring A to within about 15 degrees;

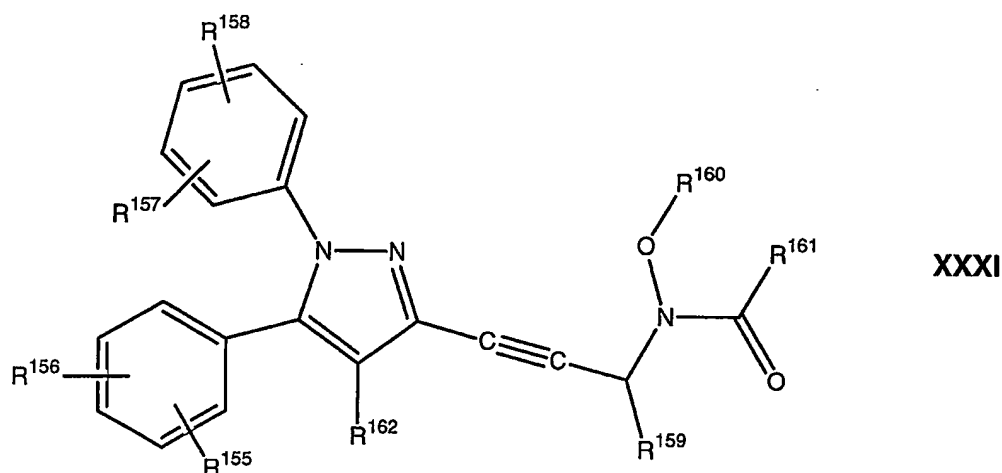
said ring D further being substituted with 1  $R^a$  group selected from the group consisting of:  $C_1 - C_2$  alkyl,  $-OC_1 - C_2$  alkyl,  $-NHC_1 - C_2$  alkyl,  $-N(C_1 - C_2 \text{ alkyl})_2$ ,  $-C(O)C_1 - C_2$  alkyl,  $-S-C_1 - C_2$  alkyl and  $-C(S)C_1 - C_2$  alkyl;

$Y^7$  represents N, CH or  $C-OC_1 - C_3$  alkyl, and when  $Z^{13}$  is N,  $Y^7$  can also represent a carbonyl group;

$R^{153}$  represents H, Br, Cl or F; and

$R^{154}$  represents H or  $CH_3$ .

**[000108]** Compounds useful as Cox-2 selective inhibitors of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI**:

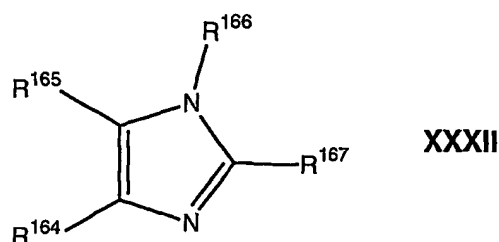


wherein:

$R^{155}$ ,  $R^{156}$ ,  $R^{157}$ , and  $R^{158}$  are independently selected from the groups consisting of hydrogen,  $C_1 - C_5$  alkyl,  $C_1 - C_5$  alkoxy, phenyl, halo, hydroxyl,  $C_1 - C_5$  alkylsulfonyl,  $C_1 - C_5$  alkylthio, trihalo $C_1 - C_5$  alkyl, amino, nitro and 2-quinolinylmethoxy;



- $R^{159}$  is hydrogen,  $C_1-C_5$  alkyl, trihalo $C_1-C_5$  alkyl, phenyl, substituted phenyl where the phenyl substituents are halogen,  $C_1-C_5$  alkoxy, trihalo $C_1-C_5$  alkyl or nitro or  $R^{159}$  is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;
- 5  $R^{160}$  is hydrogen,  $C_1-C_5$  alkyl, phenyl  $C_1-C_5$  alkyl, substituted phenyl  $C_1-C_5$  alkyl where the phenyl substituents are halogen,  $C_1-C_5$  alkoxy, trihalo $C_1-C_5$  alkyl or nitro, or  $R^{160}$  is  $C_1-C_5$  alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substituents are halogen,  $C_1-C_5$  alkoxy, trihalo $C_1-C_5$  alkyl or nitro;
- 10  $R^{161}$  is  $C_1-C_{10}$  alkyl, substituted  $C_1-C_{10}$  alkyl where the substituents are halogen, trihalo $C_1-C_5$  alkyl,  $C_1-C_5$  alkoxy, carboxy,  $C_1-C_5$  alkoxycarbonyl, amino,  $C_1-C_5$  alkylamino, di $C_1-C_5$  alkylamino, di $C_1-C_5$  alkylamino $C_1-C_5$  alkylamino,  $C_1-C_5$  alkylamino $C_1-C_5$  alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is
- 15 nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with  $C_1-C_5$  alkyl; or  $R^{161}$  is phenyl, substituted phenyl (where the phenyl substituents are one or more of  $C_1-C_5$  alkyl, halogen,  $C_1-C_5$  alkoxy, trihalo $C_1-C_5$  alkyl or nitro), or  $R^{161}$  is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused
- 20 heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or  $R^{161}$  is  $NR^{163}R^{164}$  where  $R^{163}$  and  $R^{164}$  are independently selected from hydrogen and  $C_{1-5}$  alkyl or  $R^{163}$  and  $R^{164}$  may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one
- 25 or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with  $C_1-C_5$  alkyl;  $R^{162}$  is hydrogen,  $C_1-C_5$  alkyl, nitro, amino, and halogen; and pharmaceutically acceptable salts thereof.
- [000109] Materials that can serve as a Cox-2 selective inhibitor of the
- 30 present invention include 2-substituted imidazoles that are described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula XXXII:



wherein:

R<sup>164</sup> is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

5 substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C<sub>1-5</sub> alkyl, halogen, nitro, trifluoromethyl and nitrile;

R<sup>165</sup> is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

10 substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C<sub>1</sub>–C<sub>5</sub> alkyl and halogen, or substituted phenyl,

15 wherein the substituents are independently selected from one or members of the group consisting of C<sub>1</sub>–C<sub>5</sub> alkyl, halogen, nitro, trifluoromethyl and nitrile;

R<sup>166</sup> is hydrogen, 2-(trimethylsilyl)ethoxymethyl), C<sub>1</sub>–C<sub>5</sub> alkoxycarbonyl, aryloxy carbonyl, arylC<sub>1</sub>–C<sub>5</sub> alkyl, arylC<sub>1</sub>–C<sub>5</sub> alkyl,

20 phthalimidoC<sub>1</sub>–C<sub>5</sub> alkyl, aminoC<sub>1</sub>–C<sub>5</sub> alkyl, diaminoC<sub>1</sub>–C<sub>5</sub> alkyl, succinimidoC<sub>1</sub>–C<sub>5</sub> alkyl, C<sub>1</sub>–C<sub>5</sub> alkyl carbonyl, aryl carbonyl, C<sub>1</sub>–C<sub>5</sub> alkyl carbonylC<sub>1</sub>–C<sub>5</sub> alkyl, aryloxy carbonylC<sub>1</sub>–C<sub>5</sub> alkyl, heteroarylC<sub>1</sub>–C<sub>5</sub> alkyl where the heteroaryl contains 5 to 6 ring atoms, or substituted arylC<sub>1</sub>–C<sub>5</sub> alkyl,

wherein the aryl substituents are independently selected from one or more members of the group consisting of C<sub>1</sub>–C<sub>5</sub> alkyl, C<sub>1</sub>–C<sub>5</sub> alkoxy, halogen, amino, C<sub>1</sub>–C<sub>5</sub> alkylamino, and diC<sub>1</sub>–C<sub>5</sub> alkylamino;

R<sup>167</sup> is (A<sup>11</sup>)<sub>n</sub>–(CH<sup>165</sup>)<sub>q</sub>–X<sup>24</sup> wherein:

5 A<sup>11</sup> is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X<sup>24</sup> is selected from the group consisting of hydrogen, hydroxyl, halogen, vinyl, ethynyl, C<sub>1</sub>–C<sub>5</sub> alkyl, C<sub>3</sub>–C<sub>7</sub> cycloalkyl, C<sub>1</sub>–C<sub>5</sub> alkoxy, phenoxy, phenyl, arylC<sub>1</sub>–C<sub>5</sub> alkyl, amino, C<sub>1</sub>–C<sub>5</sub> alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C<sub>1</sub>–C<sub>5</sub> alkylaminocarbonyl, phenylaminocarbonyl, arylC<sub>1</sub>–C<sub>5</sub> alkylaminocarbonyl, C<sub>1</sub>–C<sub>5</sub> alkylthio, C<sub>1</sub>–C<sub>5</sub> alkylsulfonyl, phenylsulfonyl, substituted sulfonamido,

15 wherein the sulfonyl substituent is selected from the group consisting of C<sub>1</sub>–C<sub>5</sub> alkyl, phenyl, araC<sub>1</sub>–C<sub>5</sub> alkyl, thienyl, furanyl, and naphthyl; substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

20 substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine, substituted C<sub>1</sub>–C<sub>5</sub> alkyl,

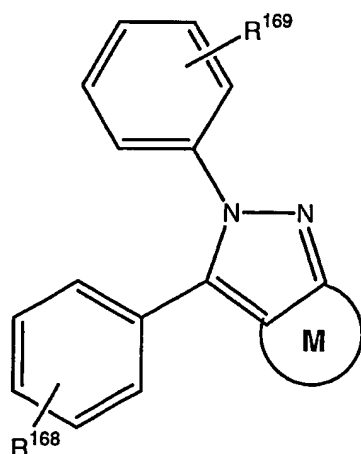
25 wherein the substituents are selected from the group consisting of one or more C<sub>1</sub>–C<sub>5</sub> alkoxy, trihaloalkyl, phthalimido and amino, substituted phenyl,

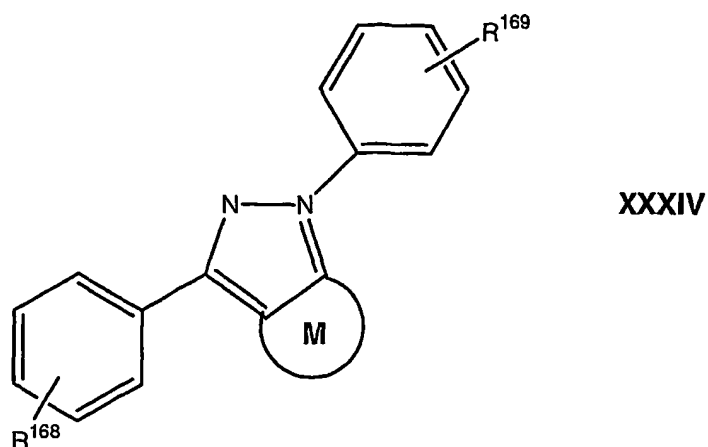
wherein the phenyl substituents are independently selected from one or more members of the group consisting of C<sub>1</sub>–C<sub>5</sub> alkyl, halogen and C<sub>1</sub>–C<sub>5</sub> alkoxy,

30 substituted phenoxy,

- wherein the phenyl substituents are independently selected from one or more members of the group consisting of C<sub>1</sub>–C<sub>5</sub> alkyl, halogen and C<sub>1</sub>–C<sub>5</sub> alkoxy,  
substituted C<sub>1</sub>–C<sub>5</sub> alkoxy,
- 5 wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,  
substituted arylC<sub>1</sub>–C<sub>5</sub> alkyl,  
wherein the alkyl substituent is hydroxyl,  
substituted arylC<sub>1</sub>–C<sub>5</sub> alkyl,
- 10 wherein the phenyl substituents are independently selected from one or more members of the group consisting of C<sub>1</sub>–C<sub>5</sub> alkyl, halogen and C<sub>1</sub>–C<sub>5</sub> alkoxy,  
substituted amido,  
wherein the carbonyl substituent is selected from the group consisting of
- 15 C<sub>1</sub>–C<sub>5</sub> alkyl, phenyl, arylC<sub>1</sub>–C<sub>5</sub> alkyl, thienyl, furanyl, and naphthyl,  
substituted phenylcarbonyl,  
wherein the phenyl substituents are independently selected from one or more members of the group consisting of C<sub>1</sub>–C<sub>5</sub> alkyl, halogen and C<sub>1</sub>–C<sub>5</sub> alkoxy,
- 20 substituted C<sub>1</sub>–C<sub>5</sub> alkylthio,  
wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,  
substituted C<sub>1</sub>–C<sub>5</sub> alkylsulfonyl,  
wherein the alkyl substituent is selected from the group consisting of
- 25 hydroxyl and phthalimido,  
substituted phenylsulfonyl,  
wherein the phenyl substituents are independently selected from one or more members of the group consisting of bromine, fluorine, chlorine, C<sub>1</sub>–C<sub>5</sub> alkoxy and trifluoromethyl,
- 30 with the proviso:

- if A<sup>11</sup> is sulfur and X<sup>24</sup> is other than hydrogen, C<sub>1</sub>–C<sub>5</sub> alkylaminocarbonyl, phenylaminocarbonyl, arylC<sub>1</sub>–C<sub>5</sub> alkylaminocarbonyl, C<sub>1</sub>–C<sub>5</sub> alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;
- if A<sup>11</sup> is sulfur and q is 1, then X<sup>24</sup> cannot be C<sub>1</sub>–C<sub>2</sub> alkyl;
- 5 if A<sup>11</sup> is carbonyl and q is 0, then X<sup>24</sup> cannot be vinyl, ethynyl, C<sub>1</sub>–C<sub>5</sub> alkylaminocarbonyl, phenylaminocarbonyl, arylC<sub>1</sub>–C<sub>5</sub> alkylaminocarbonyl, C<sub>1</sub>–C<sub>5</sub> alkylsulfonyl or phenylsulfonyl;
- if A<sup>11</sup> is carbonyl, q is 0 and X<sup>24</sup> is H, then R<sup>166</sup> is not 2-(trimethylsilyl)ethoxymethyl;
- 10 if n is 0 and q is 0, then X<sup>24</sup> cannot be hydrogen; and pharmaceutically acceptable salts thereof.
- [000110]** Materials that can serve as a Cox-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and
- 15 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:

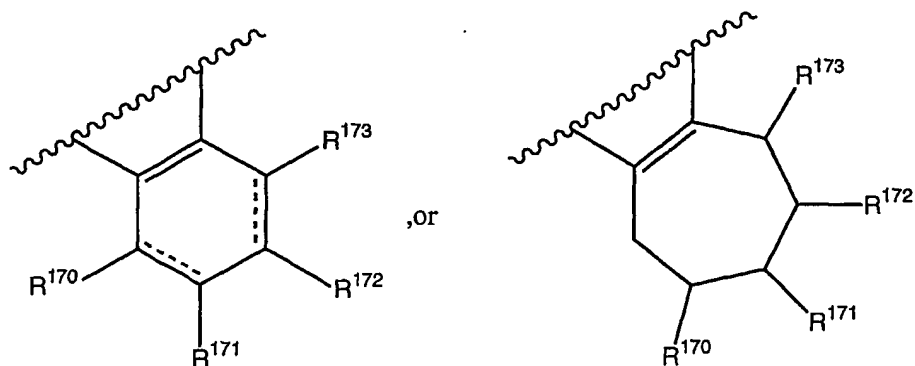
**XXXIII**



wherein:

$R^{168}$  and  $R^{169}$  are independently selected from the group consisting of hydrogen, halogen,  $(C_1 - C_6)$ alkyl,  $(C_1 - C_6)$ alkoxy, nitro, amino, hydroxyl, trifluoro,  $-S(C_1 - C_6)$ alkyl,  $-SO(C_1 - C_6)$ alkyl and  $-SO_2(C_1 - C_6)$ alkyl; and

the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



wherein:

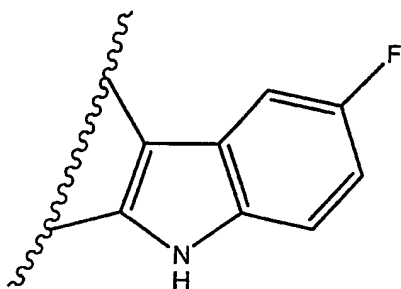
$R^{170}$  is selected from the group consisting of hydrogen, halogen, hydroxyl and carbonyl;

or  $R^{170}$  and  $R^{171}$  taken together form a moiety selected from the group consisting of  $-\text{OCOCH}_2-$ ,  $-\text{ONH}(\text{CH}_3)\text{COCH}_2-$ ,  $-\text{OCOCH=}$  and  $-\text{O}-$ ;

$R^{171}$  and  $R^{172}$  are independently selected from the group consisting of  
 5 hydrogen, halogen, hydroxyl, carbonyl, amino,  $(\text{C}_1-\text{C}_6)$ alkyl,  $(\text{C}_1-\text{C}_6)$ alkoxy,  $=\text{NOH}$ ,  $-\text{NR}^{174}\text{R}^{175}$ ,  $-\text{OCH}_3$ ,  $-\text{OCH}_2\text{CH}_3$ ,  $-\text{OSO}_2\text{NHCO}_2\text{CH}_3$ ,  $=\text{CHCO}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CO}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CON}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{CO}_2\text{NHCH}_3$ ,  $-\text{CHCHCO}_2\text{CH}_2\text{CH}_3$ ,  $-\text{OCON}(\text{CH}_3)\text{OH}$ ,  $-\text{C}(\text{COCH}_3)_2$ ,  $\text{di}(\text{C}_1-\text{C}_6)$ alkyl and  $\text{di}(\text{C}_1-\text{C}_6)$ alkoxy;

10  $R^{173}$  is selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino,  $(\text{C}_1-\text{C}_6)$ alkyl,  $(\text{C}_1-\text{C}_6)$ alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxyl, amino,  $(\text{C}_1-\text{C}_6)$ alkyl and  $(\text{C}_1-\text{C}_6)$ alkoxy;

15 or  $R^{172}$  and  $R^{173}$  taken together form a moiety selected from the group consisting of  $-\text{O}-$  and



20  $R^{174}$  is selected from the group consisting of hydrogen, OH,  $-\text{OCOCH}_3$ ,  $-\text{COCH}_3$  and  $(\text{C}_1-\text{C}_6)$ alkyl; and

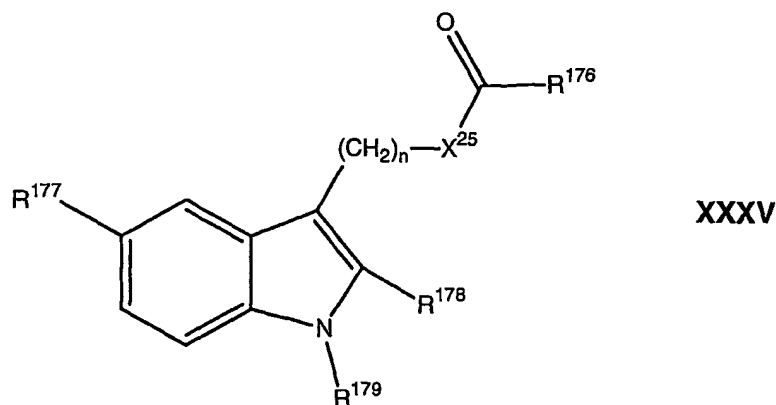
$R^{175}$  is selected from the group consisting of hydrogen, OH,  $-\text{OCOCH}_3$ ,  $-\text{COCH}_3$ ,  $(\text{C}_1-\text{C}_6)$ alkyl,  $-\text{CONH}_2$  and  $-\text{SO}_2\text{CH}_3$ ;

with the proviso that

25 if M is a cyclohexyl group, then  $R^{170}$  through  $R^{173}$  may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

[000111] Esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890 can serve as Cox-2 selective inhibitors of the present invention. Such compounds have the general formula shown below in formula XXXV:



wherein:

R<sup>176</sup> is C<sub>1</sub>–C<sub>6</sub> alkyl, C<sub>1</sub>–C<sub>6</sub> branched alkyl, C<sub>4</sub>–C<sub>8</sub> cycloalkyl, C<sub>1</sub>–C<sub>6</sub> hydroxyalkyl, branched C<sub>1</sub>–C<sub>6</sub> hydroxyalkyl, hydroxyl substituted C<sub>4</sub>–C<sub>8</sub> aryl, primary, secondary or tertiary C<sub>1</sub>–C<sub>6</sub> alkylamino, primary, secondary or tertiary branched C<sub>1</sub>–C<sub>6</sub> alkylamino, primary, secondary or tertiary C<sub>4</sub>–C<sub>8</sub> arylamino, C<sub>1</sub>–C<sub>6</sub> alkylcarboxylic acid, branched C<sub>1</sub>–C<sub>6</sub> alkylcarboxylic acid, C<sub>1</sub>–C<sub>6</sub> alkylester, branched C<sub>1</sub>–C<sub>6</sub> alkylester, C<sub>4</sub>–C<sub>8</sub> aryl, C<sub>4</sub>–C<sub>8</sub> arylcarboxylic acid, C<sub>4</sub>–C<sub>8</sub> arylester, C<sub>4</sub>–C<sub>8</sub> aryl substituted C<sub>1</sub>–C<sub>6</sub> alkyl, C<sub>4</sub>–C<sub>8</sub> heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C<sub>4</sub>–C<sub>8</sub> heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R<sup>177</sup> is C<sub>1</sub>–C<sub>6</sub> alkyl, C<sub>1</sub>–C<sub>6</sub> branched alkyl, C<sub>4</sub>–C<sub>8</sub> cycloalkyl, C<sub>4</sub>–C<sub>8</sub> aryl, C<sub>4</sub>–C<sub>8</sub> aryl-substituted C<sub>1</sub>–C<sub>6</sub> alkyl, C<sub>1</sub>–C<sub>6</sub> alkoxy, C<sub>1</sub>–C<sub>6</sub> branched alkoxy, C<sub>4</sub>–C<sub>8</sub> aryloxy, or halo-substituted versions thereof or R<sup>177</sup> is halo where halo is chloro, fluoro, bromo, or iodo;

R<sup>178</sup> is hydrogen, C<sub>1</sub>–C<sub>6</sub> alkyl or C<sub>1</sub>–C<sub>6</sub> branched alkyl;

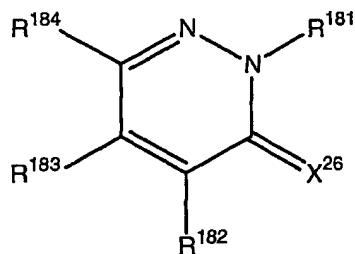


$R^{179}$  is  $C_1-C_6$  alkyl,  $C_4-C_8$  aroyl,  $C_4-C_8$  aryl,  $C_4-C_8$  heterocyclic alkyl or aryl with O, N or S in the ring,  $C_4-C_8$  aryl-substituted  $C_1-C_6$  alkyl, alkyl-substituted or aryl-substituted  $C_4-C_8$  heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted  $C_4-C_8$  aroyl, or alkyl-substituted  $C_4-C_8$  aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

$n$  is 1, 2, 3, or 4; and

$X^{25}$  is O, NH, or  $N-R^{180}$ , where  $R^{180}$  is  $C_1-C_6$  or  $C_1-C_6$  branched alkyl.

**[000112]** Materials that can serve as a Cox-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI**:



**XXXVI**

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:  $X^{26}$  is selected from the group consisting of O, S,  $-NR^{185}$ ,  $-NOR^a$ , and  $-NNR^b R^c$ ;

$R^{185}$  is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

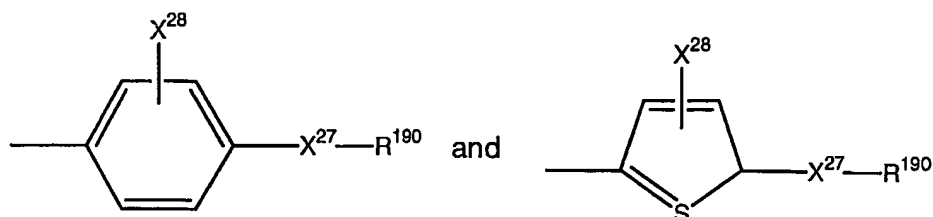
$R^a$ ,  $R^b$ , and  $R^c$  are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

$R^{181}$  is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl,

- cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy,  $-(CH_2)_n C(O)R^{186}$ ,  $-(CH_2)_n CH(OH)R^{186}$ ,  $-(CH_2)_n C(NOR^d)R^{186}$ ,  $-(CH_2)_n CH(NOR^d)R^{186}$ ,  $-(CH_2)_n CH(NR^d R^e)R^{186}$ ,  $-R^{187} R^{188}$ ,  $-(CH_2)_n C\equiv CR^{188}$ ,  $-(CH_2)_n [CH(CX^{26'}_3)]_m (CH_2)_p R^{188}$ ,  $-(CH_2)_n (CX^{26'}_2)_m (CH_2)_p R^{188}$ , and  $-(CH_2)_n (CHX^{26'})_m (CH_2)_m R^{188}$ ;
- $R^{186}$  is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;
- $R^{187}$  is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;
- $R^{188}$  is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;
- $R^d$  and  $R^e$  are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;
- $X^{26'}$  is halogen;
- m is an integer from 0-5;
- n is an integer from 0-10;
- p is an integer from 0-10;
- $R^{182}$ ,  $R^{183}$ , and  $R^{184}$  are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy,  $Y^8$ , and  $Z^{14}$ ;

provided that one of  $R^{182}$ ,  $R^{183}$ , or  $R^{184}$  must be  $Z^{14}$ , and further provided that only one of  $R^{182}$ ,  $R^{183}$ , or  $R^{184}$  is  $Z^{14}$ ;

$Z^{14}$  is selected from the group consisting of:



5

$X^{27}$  is selected from the group consisting of  $S(O)_2$ ,  $S(O)(NR^{191})$ ,  $S(O)$ ,  $Se(O)_2$ ,  $P(O)(OR^{192})$ , and  $P(O)(NR^{193}R^{194})$ ;

$X^{28}$  is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

10

$R^{190}$  is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino,  $-NHNH_2$ , and  $-NCHN(R^{191})R^{192}$ ;

$R^{191}$ ,  $R^{192}$ ,  $R^{193}$ , and  $R^{194}$  are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or  $R^{193}$  and  $R^{194}$  can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and  $NR^{188}$ ;

15

$Y^8$  is selected from the group consisting of  $-OR^{195}$ ,  $-SR^{195}$ ,  $-C(R^{197})(R^{198})R^{195}$ ,  $-C(O)R^{195}$ ,  $-C(O)OR^{195}$ ,  $-N(R^{197})C(O)R^{195}$ ,  $-NC(R^{197})R^{195}$ , and  $-N(R^{197})R^{195}$ ;

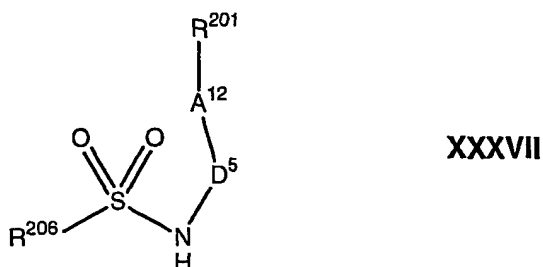
20

$R^{195}$  is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and  $NR^{199}R^{200}$ ; and

25

$R^{197}$ ,  $R^{198}$ ,  $R^{199}$ , and  $R^{200}$  are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

[000113] Benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948 are useful as Cox-2 selective inhibitors of the present invention. Such benzosulphonamide derivatives have the formula shown below in formula XXXVII:



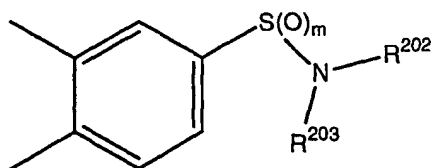
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wherein:

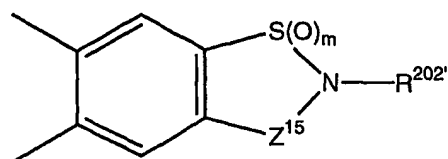
A<sup>12</sup> denotes oxygen, sulphur or NH;

R<sup>201</sup> denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF<sub>3</sub> or alkoxy;

10 D<sup>5</sup> denotes a group of formula XXXVIII or XXXIX:



or



R<sup>202</sup> and R<sup>203</sup> independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical (CH<sub>2</sub>)<sub>n</sub>-X<sup>29</sup>; or

15

R<sup>202</sup> and R<sup>203</sup> together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one

or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group  $(\text{CH}_2)_n - \text{X}^{29}$ ,  $\text{R}^{202}$  denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group  $(\text{CH}_2)_n - \text{X}^{29}$ ,

5 wherein:

$\text{X}^{29}$  denotes halogen,  $\text{NO}_2$ ,  $-\text{OR}^{204}$ ,  $-\text{COR}^{204}$ ,  $-\text{CO}_2 \text{R}^{204}$ ,  $-\text{OCO}_2 \text{R}^{204}$ ,  $-\text{CN}$ ,  $-\text{CONR}^{204} \text{OR}^{205}$ ,  $-\text{CONR}^{204} \text{R}^{205}$ ,  $-\text{SR}^{204}$ ,  $-\text{S(O)}\text{R}^{204}$ ,  $-\text{S(O)}_2 \text{R}^{204}$ ,  $-\text{NR}^{204} \text{R}^{205}$ ,  $-\text{NHC(O)}\text{R}^{204}$ ,  $-\text{NHS(O)}_2 \text{R}^{204}$ ;

10  $\text{Z}^{15}$  denotes  $-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}=\text{CH}-$ ,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CO}-$ ,  $-\text{CO}-\text{CH}_2-$ ,  $-\text{NHCO}-$ ,  $-\text{CONH}-$ ,  $-\text{NHCH}_2-$ ,  $-\text{CH}_2\text{NH}-$ ,  $-\text{N}=\text{CH}-$ ,  $-\text{NHCH}-$ ,  $-\text{CH}_2-\text{CH}_2-\text{NH}-$ ,  $-\text{CH}=\text{CH}-$ ,  $>\text{N}-\text{R}^{203}$ ,  $>\text{C}=\text{O}$ ,  $>\text{S(O)}_m$ ;  
 $\text{R}^{204}$  and  $\text{R}^{205}$  independently of each other denote hydrogen, alkyl, aralkyl or aryl;

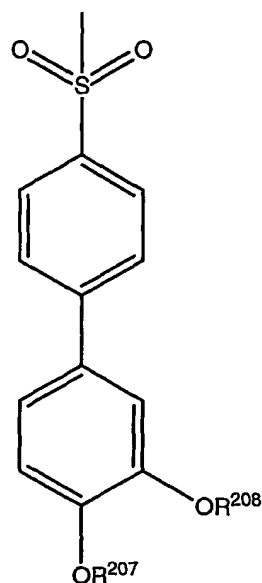
15 n is an integer from 0 to 6;

$\text{R}^{206}$  is a straight-chained or branched  $\text{C}_1 - \text{C}_4$  alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or  $\text{R}^{206}$  denotes  $\text{CF}_3$ ; and

m denotes an integer from 0 to 2;

20 with the proviso that  $\text{A}^{12}$  does not represent O if  $\text{R}^{206}$  denotes  $\text{CF}_3$ ;  
 and the pharmaceutically acceptable salts thereof.

[000114] Materials that can serve as Cox-2 selective inhibitors of the present invention include methanesulfonyl-biphenyl derivatives that are described in U.S. Patent No. 6,583,321. Such methanesulfonyl-biphenyl  
 25 derivatives have the formula shown below in formula XXXX:



XXXX

wherein:

$R^{207}$  and  $R^{208}$  are respectively a hydrogen;

$C_1$  - $C_4$ -alkyl substituted or not substituted by halogens;

5  $C_3$  - $C_7$ -cycloalkyl;

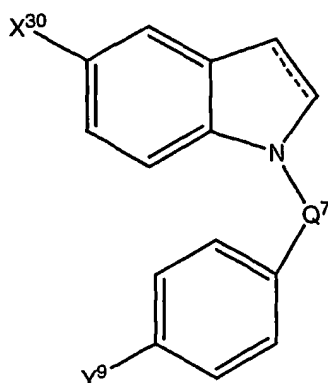
$C_1$  - $C_5$ -alkyl containing 1-3 ether bonds and/or an aryl substitute;  
substituted or not substituted phenyl;

or substituted or not substituted five or six ring-cycled heteroaryl

containing more than one hetero atoms selected from a group consisting  
10 of nitrogen, sulfur, and oxygen (wherein phenyl or heteroaryl can be one-  
or multi-substituted by a substituent selected from a group consisting of  
hydrogen, methyl, ethyl, and isopropyl).

[000115] Cox-2 selective inhibitors such as 1H-indole derivatives  
described in U.S. Patent No. 6,599,929 are useful in the present invention.

15 Such 1H-indole derivatives have the formula shown below in formula  
XXXXI:



XXXXI

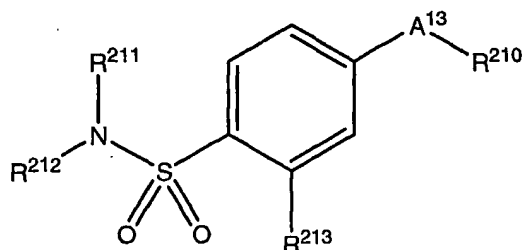
wherein:

$X^{30}$  is  $-NH\text{SO}_2R^{209}$  wherein  $R^{209}$  represents hydrogen or  $C_1-C_3$ -alkyl;

$Y^9$  is hydrogen, halogen,  $C_1-C_3$ -alkyl substituted or not substituted by halogen,  $\text{NO}_2$ ,  $\text{NH}_2$ ,  $\text{OH}$ ,  $\text{OMe}$ ,  $\text{CO}_2\text{H}$ , or  $\text{CN}$ ; and

$Q^7$  is  $\text{C}=\text{O}$ ,  $\text{C}=\text{S}$ , or  $\text{CH}_2$ .

[000116]. Compounds that are useful as Cox-2 selective inhibitors of the present invention include prodrugs of Cox-2 inhibitors that are described in U.S. Patent Nos. 6,436,967 and 6,613,790. Such prodrugs of Cox-2 inhibitors have the formula shown below in formula XXXXII:



XXXXII

wherein:

$A^{13}$  is a ring substituent selected from partially unsaturated heterocyclic, heteroaryl, cycloalkenyl and aryl, wherein  $A^{13}$  is unsubstituted or substituted with one or more radicals selected from alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxy carbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, cycloalkylalkyl, alkenyl, alkynyl, heterocycloxy, alkylthio, cycloalkyl, aryl,

heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, araalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, -arylmino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylmino, aminoalkyl, alkylaminoalkyl, N-arylminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-arylminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl;

$R^{210}$  is selected from heterocyclyl, cycloalkyl, cycloalkenyl, and aryl, wherein  $R^{210}$  is unsubstituted or substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

$R^{211}$  is selected from hydrido and alkoxycarbonylalkyl;

$R^{212}$  is selected from alkyl, carboxyalkyl, acyl, alkoxycarbonyl, heteroarylcarbonyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylcarbonyl, amino acid residue, and alkylcarbonylaminoalkylcarbonyl;

provided  $A^{13}$  is not tetrazolium, or pyridinium; and further provided  $A^{13}$  is not indanone when  $R^{212}$  is alkyl or carboxyalkyl; further provided  $A^{13}$  is not thienyl, when  $R^{210}$  is 4-fluorophenyl, when  $R^{211}$  is hydrido, and when  $R^{212}$  is methyl or acyl; and

$R^{213}$  is hydrido;

or a pharmaceutically-acceptable salt thereof.

**[000117]** Specific non-limiting examples of substituted sulfonamide prodrugs of Cox-2 inhibitors disclosed in U.S. Patent No. 6,436,967 that are useful in the present invention include:

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]propanamide;

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;



- N-[[4-[1,5-dimethyl)-3-phenyl-1H-pyrazol-4-yl]phenyl]sulfonyl]acetamide;  
N-[[4-(2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)phenyl]sulfonyl]acetamide;  
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;  
5 N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;  
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;  
10 N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;  
N-[[4-[2-(3-chloro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;  
N-[[4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]phenyl]sulfonyl]acetamide;  
15 2-methyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;  
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;  
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]benzamide;  
2,2-dimethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;  
20 N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide;  
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]pentanamide;  
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]hexanamide;  
3-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide ;  
25 2-ethoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;  
N-[[4-[5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;  
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]propanamide;  
30 N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;

- N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
- N-[[4-[3-(difluoromethyl)-6-fluoro-1,5-dihydro-7-methoxy-[2]benzothiopyrano [4,3-c]pyrazol-1-yl)phenyl]sulfonyl]acetamide;
- 5 N-[[4-[6-fluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyran o[4,3-c]pyrazol-1-yl]phenyl]sulfonyl]acetamide;
- N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
- N-[[4-(2-methyl-4-phenyloxazol-5-yl)phenyl]sulfonyl]acetamide;
- 10 methyl[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]oxoacetate;
- 2-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
- N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
- 15 N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]butanamide;
- N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]formamide;
- 1,1-dimethylethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
- 20 N-[[<sup>4</sup>-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine;
- 2-amino-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
- 2-(acetyl amino)-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
- methyl 4-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-4-
- 25 oxobutanoate;
- methyl N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
- N-acetyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine, ethyl ester;
- N-[[4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]sulfonyl]acetamide;
- 30 methyl 3-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-3-oxopropanoate;

- 4-[5-(3-bromo-5-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)oxazol-4-yl]-N-methylbenzenesulfonamide;  
 N-(1,1-dimethylethyl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;  
 5 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-methylbenzenesulfonamide;  
 N-methyl-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;  
 N-[[4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;  
 N-[[4-[5-(acetoxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;  
 10 N-[[4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]phenyl]sulfonyl]acetamide;  
 4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]-N-methylbenzenesulfonamide;  
 N-[[4-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)phenyl]sulfonyl]propanamide;  
 N-[[4-[2-(2-methylpyridin-3-yl)-4-trifluoromethylimidazol-1-yl]phenyl]sulfonyl]propanamide;  
 15 4-[2-(4-fluorophenyl)cyclopenten-1-yl]-N-methylbenzenesulfonamide; and  
 N-[[4-(3-phenyl-2,3-dihydro-2-oxofuran-4-yl)phenyl]sulfonyl]propanamide.  
**[000118]** Those prodrugs disclosed in U.S. Patent No. 6,613,790 have the general formula shown above in formula **XXXXII** wherein:  
 20  $A^{13}$  is a pyrazole group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, intro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulonyloxy,  
 25 alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, alkenyl, alkynyl, alkylthio, alkylthioalkyl, alkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkylsutfinyl, alkylsulfonyl, aminosulfonyl, and alkylaminosulfonyl;  
 30  $R^{210}$  is a phenyl group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl,

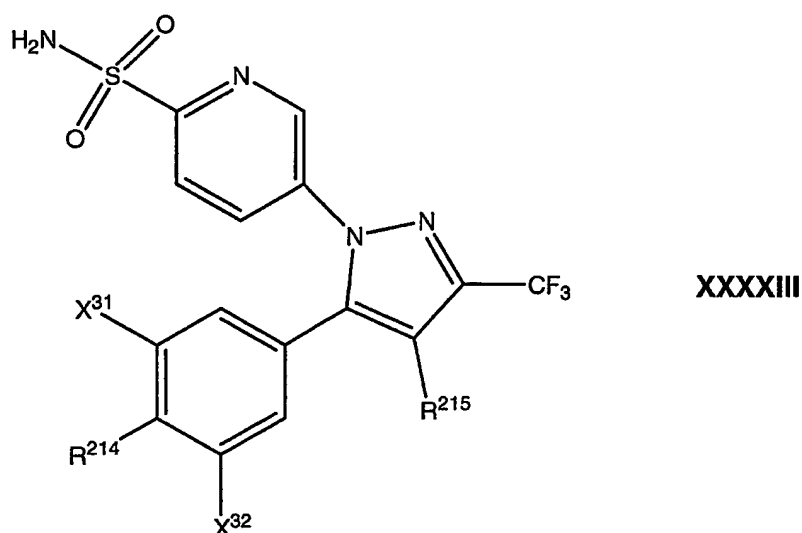
hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

$R^{211}$  and  $R^{212}$  are independently selected from the group consisting of hydroxyalkyl and hydrido but at least one of  $R^{211}$  and  $R^{212}$  is other than hydrido; and

$R^{213}$  is selected from the group consisting of hydrido and fluoro.

**[000119]** Examples of prodrug compounds disclosed in U.S. 6,613,790 that are useful as Cox-2 inhibitors of the present invention include, but are not limited to, N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, or pharmaceutically-acceptable salts thereof.

**[000120]** Cox-2 selective inhibitors such as sulfamoylheleroaryl pyrazole compounds that are described in U.S. Patent No. 6,583,321 may serve as Cox-2 inhibitors of the present invention. Such sulfamoylheleroaryl pyrazole compounds have the formula shown below in formula **XXXXIII**:



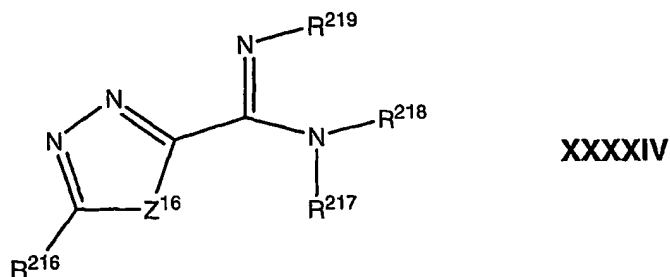
wherein:

$R^{214}$  is furyl, thiazolyl or oxazolyl;

$R^{215}$  is hydrogen, fluoro or ethyl; and

$X^{31}$  and  $X^{32}$  are independently hydrogen or chloro.

[000121] Heteroaryl substituted amidinyl and imidazolyl compounds such as those described in U.S. Patent No. 6,555,563 are useful as Cox-2 selective inhibitors of the present invention. Such heteroaryl substituted amidinyl and imidazolyl compounds have the formula shown below in formula XXXXIV:



wherein:

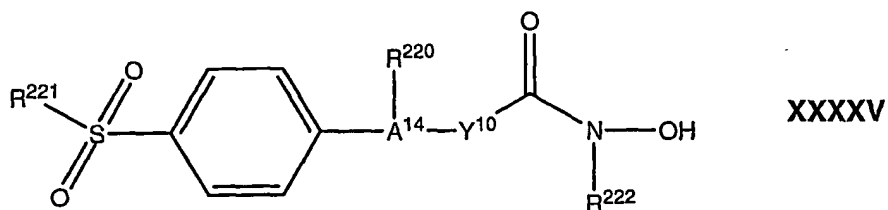
Z<sup>16</sup> is O or S,

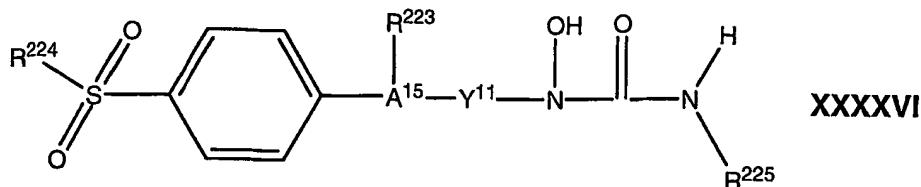
R<sup>216</sup> is optionally substituted aryl,

R<sup>217</sup> is aryl optionally substituted with aminosulfonyl, and

R<sup>218</sup> and R<sup>219</sup> cooperate to form an optionally substituted 5-membered ring.

[000122] Materials that can serve as Cox-2 selective inhibitors of the present invention include substituted hydroxamic acid derivatives that are described in U.S. Patent Nos. 6,432,999, 6,512,121, and 6,515,014. These compounds also act as inhibitors of the lipoxxygenase-5 enzyme. Such substituted hydroxamic acid derivatives have the general formulas shown below in formulas XXXXV and XXXXVI:





**[000123]** Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 have the formula shown above in formula **XXXXV**, wherein:

- 5     A<sup>14</sup> is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;
- Y<sup>10</sup> is selected from lower alkenylene and lower alkynylene;
- 10    R<sup>220</sup> is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R<sup>220</sup> is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower
- 15    haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;
- R<sup>221</sup> is selected from lower alkyl and amino; and
- R<sup>222</sup> is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt
- 20    thereof.

**[000124]** Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 may also have the formula shown above in formula **XXXXVI**, wherein:

- 25    A<sup>15</sup> is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;
- Y<sup>11</sup> is selected from lower alkylene, lower alkenylene and lower alkynylene;

$R^{223}$  is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein  $R^{223}$  is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylimino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

$R^{224}$  is selected from lower alkyl and amino; and

$R^{225}$  is selected from hydrido, lower alkyl;

or a pharmaceutically-acceptable salt thereof.

**[000125]** Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 have the formula shown above in formula **XXXXV**, wherein:

$A^{14}$  is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isochiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein  $A^{14}$  is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

$Y^{10}$  is lower alkylene, lower alkenylene, and lower alkynylene;

$R^{220}$  is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein  $R^{220}$  is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

$R^{221}$  is selected from lower alkyl and amino; and

$R^{222}$  is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

**[000126]** Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 may also have the formula shown above in formula **XXXXVI**, wherein:

- 5  $A^{15}$  is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isothiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;
- 10  $Y^{11}$  is selected from lower alkyl, lower alkenyl and lower alkynyl;
- $R^{223}$  is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein  $R^{223}$  is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl,
- 15 cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;
- $R^{224}$  is selected from lower alkyl and amino; and
- $R^{225}$  is selected from hydrido and alkyl; or a pharmaceutically-acceptable
- 20 salt thereof.

**[000127]** Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 have the formula shown above in formula **XXXXV**, wherein:

- 25  $A^{14}$  is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;
- $Y^{10}$  is ethylene, isopropylene, propylene, butylene, lower alkenylene, and lower alkynylene;
- 30  $R^{220}$  is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein  $R^{220}$  is optionally substituted at a substitutable position



with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

5  $R^{221}$  is selected from lower alkyl and amino; and

$R^{222}$  is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

10 **[000128]** Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 may also have the formula shown above in formula **XXXXV**, wherein:

$A^{15}$  is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

15  $Y^{11}$  is selected from lower alkyl, lower alkenyl and lower alkynyl;

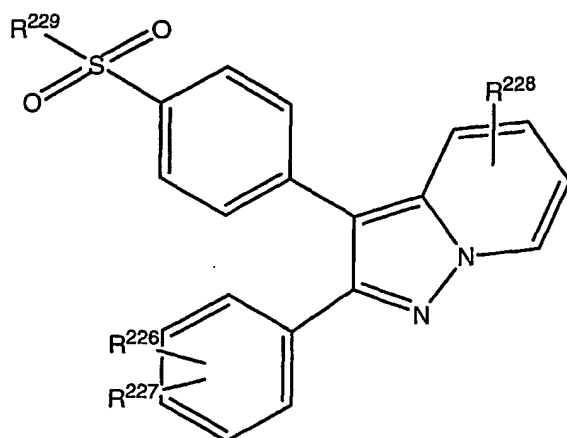
$R^{223}$  is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein  $R^{223}$  is optionally substituted at a substitutable position

20 with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

$R^{224}$  is selected from lower alkyl and amino; and

25  $R^{225}$  is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

**[000129]** Compounds that are useful as Cox-2 selective inhibitors of the present invention include pyrazolopyridine compounds that are described in U.S. Patent No. 6,498,166. Such pyrazolopyridine compounds have the  
30 formula shown below in formula **XXXXVII**:



XXXXVII

wherein:

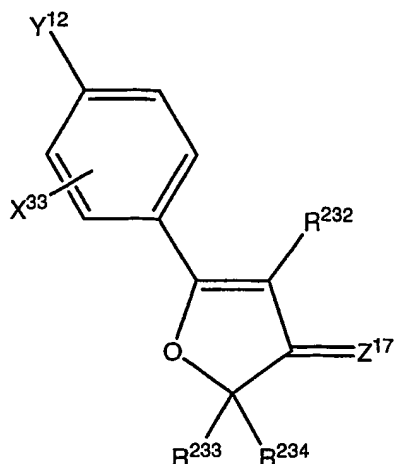
$R^{226}$  and  $R^{227}$  are independently selected from the group consisting of H, halogen,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy, and  $C_1-C_6$  alkoxy substituted by one or more fluorine atoms;

$R^{228}$  is halogen, CN, CON  $R^{230}$   $R^{231}$ ,  $CO_2$  H,  $CO_2$   $C_1-C_6$  alkyl, or  $NHSO_2R^{230}$ ;

$R^{229}$  is  $C_1-C_6$  alkyl or  $NH_2$ ; and

$R^{225}$  and  $R^{225}$  are independently selected from the group consisting of H,  $C_1-C_6$  alkyl, phenyl, phenyl substituted by one or more atoms or groups selected from the group consisting of halogen,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy, and  $C_1-C_6$  alkoxy substituted by one or more fluorine atoms, or a pharmaceutically acceptable salt, solvate, ester, or salt or solvate of such ester thereof.

**[000130]** Materials that are useful as Cox-2 selective inhibitors of the present invention include 4,5-diaryl-3(2H)-furanone derivatives that are described in U.S. Patent No. 6,492,416. Such 4,5-diaryl-3(2H)-furanone derivatives have the formula shown below in formula XXXXVIII:



XXXXVIII

wherein:

X<sup>33</sup> represents halo, hydrido, or alkyl;

Y<sup>12</sup> represents alkylsulfonyl, aminosulfonyl, alkylsulfinyl, (N-acylamino)-sulfonyl, (N-alkylamino)sulfonyl, or alkylthio;

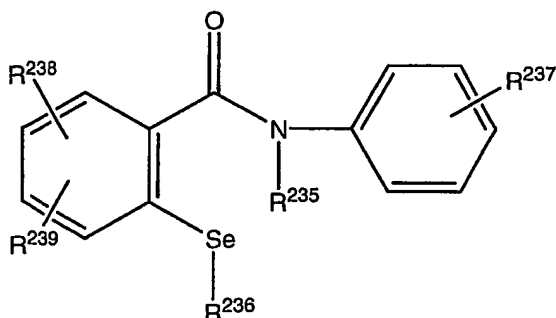
Z<sup>17</sup> represents oxygen or sulfur atom;

R<sup>233</sup> and R<sup>234</sup> are selected independently from lower alkyl radicals;

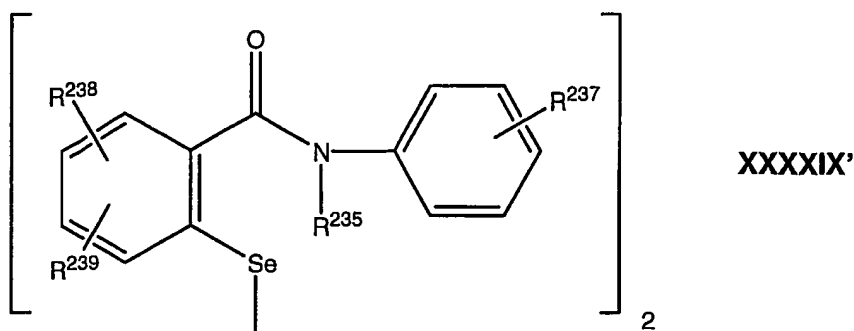
and R<sup>232</sup> represents a substituted or non-substituted aromatic group of 5 to 10 atoms;

or a pharmaceutically-acceptable salt thereof.

[000131] Cox-2 selective inhibitors that can be used in the present invention include 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives that are described in U.S. Patent No. 6,492,416. Such 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives have the formulas shown below in formulas XXXXIX or XXXXIX':



XXXXIX



wherein:

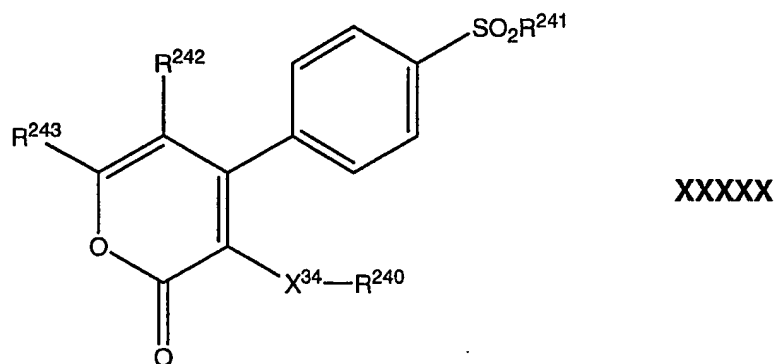
$R^{235}$  is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

$R^{236}$  is a hydrogen atom, a hydroxyl group, an organothiol group that is bound to the selenium atom by its sulfur atom, or  $R^{235}$  and  $R^{236}$  are joined to each other by a single bond;

$R^{237}$  is a hydrogen atom, a halogen atom, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, a trifluoromethyl group, or a nitro group;

$R^{238}$  and  $R^{239}$  are identical to or different from each other, and each is a hydrogen atom, a halogen atom, an alkoxy group having 1-4 carbon atoms, a trifluoromethyl group, or  $R^{238}$  and  $R^{239}$  are joined to each other to form a methylenedioxy group, a salt thereof, or a hydrate thereof.

**[000132]** Pyrones such as those disclosed in U.S. Patent No. 6,465,509 are also useful as Cox-2 inhibitors of the present invention. These pyrone compounds have the general formula shown below in formula **XXXXX**:



wherein:

$X^{34}$  is selected from the group consisting of:

- (a) a bond,
- (b)  $--(CH_2)_m--$ , wherein m 1 or 2,
- (c)  $--C(O)--$ ,
- 5 (d)  $--O--$ ,
- (e)  $--S--$ , and
- (f)  $--N(R^{244})--$ ;

$R^{240}$  is selected from the group consisting of:

- (a)  $C_1 - C_{10}$  alkyl, optionally substituted with 1-3 substituents independently
- 10 selected from the group consisting of: hydroxy, halo,  $C_1 - C_{10}$  alkoxy,  $C_1 - C_{10}$  alkylthio, and CN,
- (b) phenyl or naphthyl, and
- (c) heteroaryl, which is comprised of a monocyclic aromatic ring of 5
- atoms having one hetero atom which is S, O or N, and optionally 1, 2, or 3
- 15 additional N atoms; or
- a monocyclic ring of 6 atoms having one hetero atom which is N, and
- optionally 1, 2, or 3 additional N atoms, wherein groups (b) and (c) above
- are each optionally substituted with 1-3 substituents independently
- selected from the group consisting of: halo,  $C_1 - C_{10}$  alkoxy,  $C_1 - C_{10}$
- 20 alkylthio, CN,  $C_1 - C_{10}$  alkyl, optionally substituted to its maximum with
- halo, and  $N_3$ ;

$R^{241}$  is selected from the group consisting of

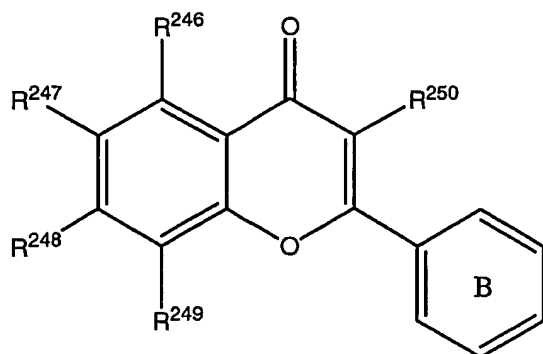
- (a)  $C_1 - C_6$  alkyl, optionally substituted to its maximum with halo,
  - (b)  $NH_2$ , and
  - 25 (c)  $NHC(O)C_1 - C_{10}$  alkyl, optionally substituted to its maximum with halo;
- $R^{242}$  and  $R^{243}$  are each independently selected from the group consisting of: hydrogen, halo, and  $C_1 - C_6$  alkyl, optionally substituted to its maximum with halo; and

- 30  $R^{244}$  is selected from the group consisting of: hydrogen and  $C_1 - C_6$  alkyl, optionally substituted to its maximum with halo.

**[000133]** Examples of pyrone compounds that are useful as Cox-2 selective inhibitors of the present invention include, but are not limited to:

- 4-(4-Methylsulfonyl)phenyl-3-phenyl-pyran-2-one,  
 3-(4-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,  
 3-(3-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,  
 6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,  
 5 6-Difluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,  
 6-Fluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,  
 6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenylthio-pyran-2-one,  
 6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenoxy-pyran-2-one,  
 6-Methyl-4-(4-methylsulfonyl)phenyl-3-pyridin-3-yl-pyran-2-one,  
 10 3-Isopropylthio-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,  
 4-(4-Methylsulfonyl)phenyl)-3-phenylthio-6-trifluoromethyl-pyran-2-one,  
 3-Isopropylthio-4-(4-methylsulfonyl)phenyl-6-trifluoromethyl-pyran-2-one,  
 4-(4-Methylsulfonyl)phenyl-3-phenyl-6-(2,2,2-trifluoroethyl)-pyran-2-one,  
 and  
 15 3-(3-Hydroxy-3-methylbutyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one.

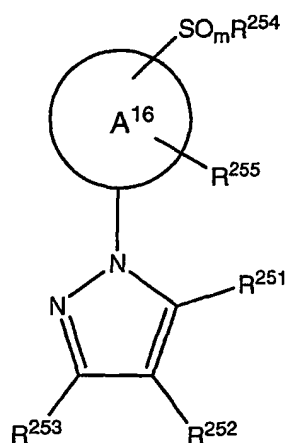
**[000134]** Organically synthesized or purified from plant sources, free-B-ring flavanoids such as those described in U.S. Published Application No. 2003/0165588, are useful as Cox-2 selective inhibitors of the present  
 20 invention. Such free-B-ring flavanoids have the general structure shown in formula **XXXXXI**:

**XXXXXI**

wherein:

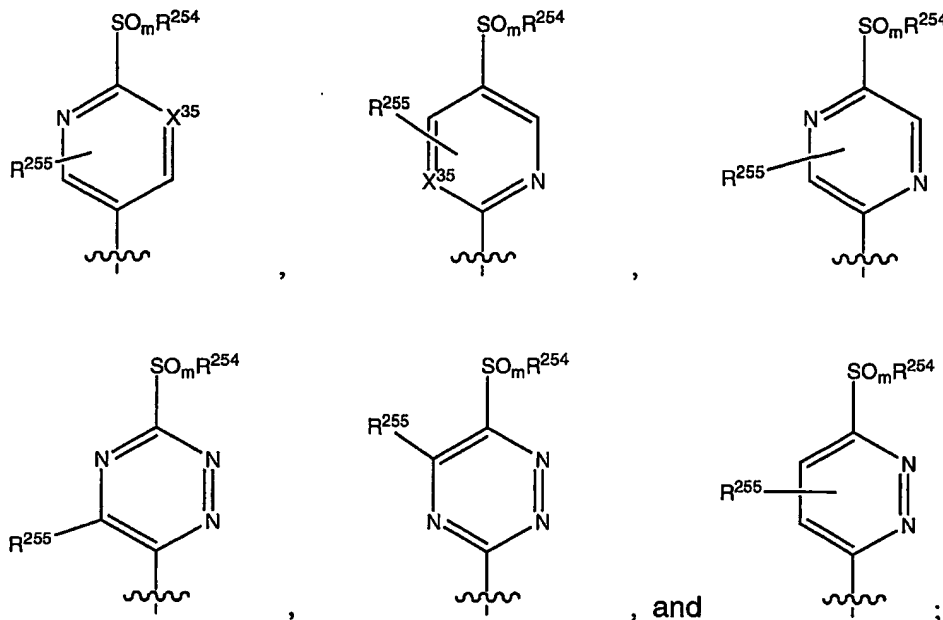
$R^{246}$ ,  $R^{247}$ ,  $R^{248}$ ,  $R^{249}$ , and  $R^{250}$  are independently selected from the group consisting of: --H, --OH, --SH, --OR, --SR, --NH<sub>2</sub>, --NHR<sup>245</sup>, --N(R<sup>245</sup>)<sub>2</sub>, --N(R<sup>245</sup>)<sub>3</sub><sup>+</sup>X<sup>35-</sup>, a carbon, oxygen, nitrogen or sulfur, glycoside of a single or a combination of multiple sugars including, aldopentoses, methyl-aldopentose, aldohexoses, ketohexose and their chemical derivatives thereof; wherein  $R^{245}$  is an alkyl group having between 1-10 carbon atoms; and  $X^{35}$  is selected from the group of pharmaceutically acceptable counter anions including, hydroxyl, chloride, iodide, sulfate, phosphate, acetate, fluoride and carbonate.

**[000135]** Heterocyclo-alkylsulfonyl pyrazoles such as those described in European Patent Application No. EP 1312367 are useful as Cox-2 selective inhibitors of the present invention. Such heterocyclo-alkylsulfonyl pyrazoles have the general formula shown below in formula **XXXXXXII**:

**XXXXXXII**

or a pharmaceutically acceptable salt thereof, wherein:

the ring of the formula (R<sup>255</sup>)-A-(SO<sub>m</sub>R<sup>254</sup>) is selected from the group consisting of:



$m$  is 0, 1 or 2;

5  $X^{35}$  is  $>CR^{255}$  or  $>N$ ;

$R^{251}$  is a radical selected from the group consisting of H,  $NO_2$ , CN,  $(C_1 - C_6)alkyl$ ,  $(C_1 - C_6)alkyl-SO_2-$ ,  $(C_6 - C_{10})aryl-SO_2-$ ,  $H-(C=O)-$ ,  $(C_1 - C_6)alkyl-(C=O)-$ ,  $(C_1 - C_6)alkyl-(C=O)-$ ,  $(C_1 - C_9)heteroaryl-(C=O)-$ ,  $(C_1 - C_9)heterocyclyl-(C=O)-$ ,  $H_2N-(C=O)-$ ,  $(C_1 - C_6)alkyl-NH-(C=O)-$ ,  $[(C_1 - C_6)alkyl]_2-N-(C=O)-$ ,  $[(C_6 - C_{10})aryl]_2-NH-(C=O)-$ ,  $[(C_1 - C_6)alkyl]-[(C_6 - C_{10})aryl-N]-(C=O)-$ ,  $HO-NH-(C=O)-$ , and  $(C_1 - C_6)alkyl-O-NH-(C=O)-$ ;

10  $R^{252}$  is a radical selected from the group consisting of H,  $-NO_2$ ,  $-CN$ ,  $(C_2 - C_6)alkenyl$ ,  $(C_2 - C_6)alkynyl$ ,  $(C_3 - C_7)cycloalkyl$ ,  $(C_6 - C_{10})aryl$ ,  $(C_1 - C_9)heteroaryl$ ,  $(C_1 - C_9)heterocyclyl$ ,  $(C_1 - C_6)alkyl-O-$ ,  $(C_3 - C_7)cycloalkyl-O-$ ,  $(C_6 - C_{10})aryl-O-$ ,  $(C_1 - C_9)heteroaryl-O-$ ,  $(C_6 - C_9)heterocyclyl-O-$ ,  $H-(C=O)-$ ,  $(C_1 - C_6)alkyl-(C=O)-$ ,  $(C_3 - C_7)cycloalkyl-(C=O)-$ ,  $(C_6 - C_{10})aryl-(C=O)-$ ,  $(C_1 - C_9)heteroaryl-(C=O)-$ ,  $(C_1 - C_9)heterocyclyl-(C=O)-$ ,  $(C_1 - C_6)alkyl-O-(C=O)-$ ,  $(C_3 - C_7)cycloalkyl-O-(C=O)-$ ,  $(C_6 - C_{10})aryl-O-(C=O)-$ ,  $(C_1 - C_9)heteroaryl-O-(C=O)-$ ,  $(C_1 - C_9)heterocyclyl-O-(C=O)-$ ,  $(C_1 - C_6)alkyl-(C=O)-O-$ ,  $(C_3 - C_7)cycloalkyl-(C=O)-O-$ ,  $(C_6 - C_{10})aryl-(C=O)-O-$ ,  $(C_1 - C_9)heteroaryl-(C=O)-O-$ ,  $(C_1 - C_9)heterocyclyl-(C=O)-O-$ ,  $(C_1 - C_6)alkyl-(C=O)-NH-$ ,  $(C_3 - C_7)cycloalkyl-(C=O)-NH-$ ,  $(C_6 - C_{10})aryl-(C=O)-NH-$ ,  $(C_1 - C_9)heteroaryl-(C=O)-NH-$ ,  $(C_1 -$



- C<sub>9</sub>)heterocyclyl-(C=O)-NH-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-(C=O)-NH-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-NH-,  
 [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>-N-, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl-NH-, [(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl]<sub>2</sub>-N-, [(C<sub>6</sub>-  
 C<sub>10</sub>)aryl]-NH-, [(C<sub>6</sub>-C<sub>10</sub>)aryl]<sub>2</sub>-N-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-[(C<sub>6</sub>-C<sub>10</sub>)aryl]-N-, [(C<sub>1</sub>-  
 C<sub>9</sub>)heteroaryl]-NH-, [(C<sub>1</sub>-C<sub>9</sub>)heteroaryl]<sub>2</sub>-N-, [(C<sub>1</sub>-C<sub>9</sub>)heterocyclyl]-NH-, [(C<sub>1</sub>-  
 C<sub>9</sub>)heterocyclyl]<sub>2</sub>-N-, H<sub>2</sub>N-(C=O)-, HO-NH-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-NH-  
 (C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-NH-(C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>-N-(C=O)-, [(C<sub>3</sub>-  
 C<sub>7</sub>)cycloalkyl]-NH-(C=O)-, [(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl]<sub>2</sub>-N-(C=O)-, [(C<sub>6</sub>-C<sub>10</sub>)aryl]-NH-  
 (C=O)-, [(C<sub>6</sub>-C<sub>10</sub>)aryl]<sub>2</sub>-N-(C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-[(C<sub>6</sub>-C<sub>10</sub>)aryl]-N-(C=O)-,  
 [(C<sub>1</sub>-C<sub>9</sub>)heteroaryl]-NH-(C=O)-, [(C<sub>1</sub>-C<sub>9</sub>)heteroaryl]<sub>2</sub>-N-(O=O)-, [(C<sub>1</sub>-  
 C<sub>9</sub>)heterocyclyl]-NH-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S- and (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally  
 substituted by one -OH substituent or by one to four fluoro substituents;  
 R<sup>253</sup> is a saturated (3- to 4-membered)-heterocyclyl ring radical; or a  
 saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl  
 ring radical;
- wherein said saturated (3- to 4-membered)-heterocyclyl ring radical  
 or said saturated, partially saturated or aromatic (7- to 9-membered)-  
 heterocyclyl ring radical; may optionally contain one to four ring  
 heteroatoms independently selected from the groups consisting of -N=,  
 -NH-, -O- and -S-;
- wherein said saturated (3- to 4-membered)-heterocyclyl ring  
 radical; or said saturated, partially saturated or aromatic (7- to 9-  
 membered)-heterocyclyl ring radical; may optionally be substituted on any  
 ring carbon atom by one to three substituents per ring independently  
 selected from the group consisting of halo, -OH, -CN, -NO<sub>2</sub>, (C<sub>2</sub>-  
 C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>2</sub>-  
 C<sub>9</sub>)heterocyclyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-, H-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-(C=O)-, HO-  
 (C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-(C=O)-, -NH<sub>2</sub>, (C<sub>1</sub>-C<sub>6</sub>)alkyl-NH-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>-N-,  
 (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl-NH-, (C<sub>6</sub>-C<sub>10</sub>)aryl-NH-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-[(C<sub>6</sub>-C<sub>10</sub>)aryl]-N-,  
 (C<sub>1</sub>-C<sub>9</sub>)heteroaryl-NH-, H<sub>2</sub>N-(C=O)-[(C<sub>1</sub>-C<sub>6</sub>)alkyl]-NH-(C=O)-, [(C<sub>1</sub>-  
 C<sub>6</sub>)alkyl]<sub>2</sub>-N-(C=O)-, [(C<sub>6</sub>-C<sub>10</sub>)aryl]-NH-(C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-[(C<sub>6</sub>-C<sub>10</sub>)aryl]-  
 N-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-NH-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-(C=O)-HN-, (C<sub>1</sub>-  
 C<sub>6</sub>)alkyl-(C=O)-[(C<sub>1</sub>-C<sub>6</sub>)alkyl-N]-, -SH, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S-,

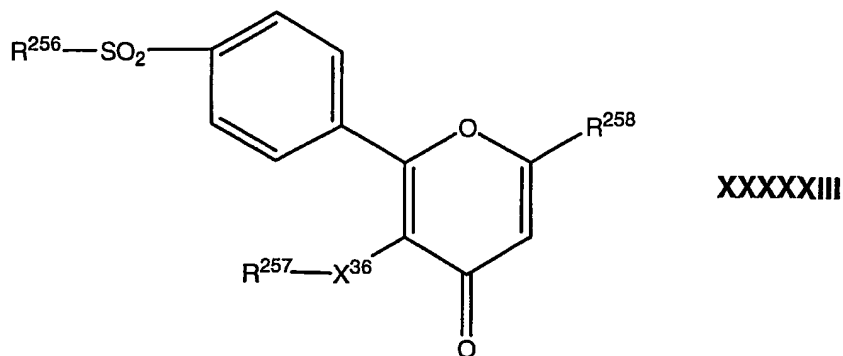
(C<sub>1</sub>-C<sub>6</sub>)alkyl-(S=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-SO<sub>2</sub>- and (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with one to four fluoro moieties;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-  
 5 membered)-heterocyclyl ring radical; may also optionally be substituted on any ring nitrogen atom by one to three substituents per ring independently selected from the group consisting of (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>2</sub>-C<sub>9</sub>)heterocyclyl, H-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-(C=O)-, H<sub>2</sub>N-(C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-NH-(C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>-N-(C=O)-, [(C<sub>6</sub>-  
 10 C<sub>10</sub>)aryl]-NH-(C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-[[(C<sub>6</sub>-C<sub>10</sub>)aryl]-N]-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-NH-(C=O)-, and (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with one to four fluoro moieties;

R<sup>254</sup> is an (C<sub>1</sub>-C<sub>6</sub>)alkyl radical optionally substituted by one to four fluoro substituents; and

15 R<sup>255</sup> is a radical selected from the group consisting of H, halo, -OH, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, -CN, H-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-(C=O)-O-, HO-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-NH-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>-N-, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl-NH-, (C<sub>6</sub>-C<sub>10</sub>)aryl-NH-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-[[(C<sub>6</sub>-C<sub>10</sub>)aryl]-N]-, (C<sub>1</sub>-C<sub>9</sub>)heteroaryl-NH-, H<sub>2</sub>N-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-NH-(C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>-N-(C=O)-, (C<sub>6</sub>-  
 20 C<sub>10</sub>)aryl-(C=O)-, [(C<sub>1</sub>-C<sub>6</sub>)alkyl]-[[(C<sub>6</sub>-C<sub>10</sub>)aryl]-N]-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-O-NH-(C=O)-, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S-, and (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by one to four fluoro substituents.

[000136] 2-phenylpyran-4-one derivatives such as those described in  
 25 U.S. Patent No. 6,518,303 are also useful as Cox-2 selective inhibitors of the present invention. Such 2-phenylpyran-4-one derivatives have the general formula shown below in formula XXXXXIII:



wherein:

$R^{256}$  represents an alkyl or  $-NR^{259}R^{260}$  group, wherein  $R^{259}$  and  $R^{260}$  each independently represents a hydrogen atom or an alkyl group;

5  $R^{257}$  represents an alkyl,  $C_3-C_7$  cycloalkyl, naphthyl, tetrahydronaphthyl or indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

10  $R^{258}$  represents a methyl, hydroxymethyl, alkoxymethyl,  $C_3-C_7$  cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a  $CH_2-R^{261}$  group wherein  $R^{261}$  represents an alkyl group; and

15  $X^{36}$  represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

**[000137]** Examples of 2-phenylpyran-4-one derivatives useful in the present invention include, but are not limited to:

3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,  
 20 3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,  
 3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,  
 3-(4-bromophenyl)-2-(4-methylsulfonylphenyl)-6-methylpyran-4-one,  
 3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,  
 3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,  
 25 3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one ,

- 2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxy pyran-4-one,  
 3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,  
 3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,  
 3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,  
 5 3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,  
 3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,  
 2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy)pyran-4-one,  
 3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,  
 10 3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,  
 3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one,  
 3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-one,  
 15 and pharmaceutically acceptable salts thereof.
- [000138]** Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent No. 6,472,416 (sulfonylphenylpyrazoles); U.S. Patent No. 6,451,794 (2,3-diaryl-pyrazolo[1,5-b]pyridazines); U.S. Patent Nos. 20 6,169,188, 6,020,343, and 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); and U.S. Patent Nos. 6,359,182 and 25 6,538,116 (C-nitroso compounds).
- [000139]** Examples of specific compounds that are useful as Cox-2 selective inhibitors include, without limitation:
- a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;  
 30 a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;  
 a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

- a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;
- a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
- 5 a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
- a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- 10 a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- 15 b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide
- b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 20 b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 25 b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 30 c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

- c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 15 d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
- d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 20 d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 25 d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 30 d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
- d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

- e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;  
e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;  
e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;  
5 e4) 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;  
e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;  
10 e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;  
e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;  
e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;  
15 e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;  
e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;  
20 f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;  
f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;  
f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
25 f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
30 f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

- f7) 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 5 f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 10 g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
- 15 g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
- g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 20 g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 25 g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 30 h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;



- h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 5 h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 10 h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- h9) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
- i1) N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
- 15 i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
- i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
- 20 i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
- i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;
- 25 i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
- i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 30 i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

- i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
- j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 5 j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
- j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
- j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
- j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
- 10 j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
- j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 15 k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 20 k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 25 k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
- k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
- 30 k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

- l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 5 l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
- l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- 10 l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
- l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;
- l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
- 15 l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
- l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
- m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
- and
- 20 m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.
- m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

- m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o4) 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
- o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 p4) 6-[(phenylmethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 q1) 8-chloro-6-[(phenylmethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;
- r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
- r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 15 r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
- 20 r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
- r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 25 r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
- s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or
- 30 s3) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl]-4-oxazolyl]benzenesulfonamide;
- or a pharmaceutically acceptable salt or prodrug thereof.

[000140] Cox-2 inhibitors that are useful in the methods and compositions of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable. Likewise, Cox-2 inhibitors that are useful in the compositions and methods of present invention can be synthesized, for example, according to the description in **Example 1**. Several Cox-2 inhibitors that are suitable for use with the compositions and methods of the present invention may be synthesized by the methods described in, for example, U.S. Patent No. 5,466,823 to Talley, *et al.* Cox-2 inhibitors can also be isolated and purified from natural sources. Cox-2 inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[000141] Preferred Cox-2 selective inhibitor compounds are those compounds selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, RS 57067, T-614, BMS-347070 (Bristol Meyers Squibb, described in U.S. Patent No. 6,180,651), JTE-522 (Japan Tobacco), S-2474 (Shionogi), SVT-2016, CT-3 (Atlantic Pharmaceutical), ABT-963 (Abbott), SC-58125 (GD Searle), nimesulide, flosulide, NS-398 (Taisho Pharmaceutical), L-745337 (Merck), RWJ-63556, L-784512 (Merck), darbufelone (Pfizer), CS-502 (Sankyo), LAS-34475 (Almirall Prodesfarma), LAS-34555 (Almirall Prodesfarma), S-33516 (Servier), SD-8381 (Pharmacia, described in U.S. Patent No. 6,034,025), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1376 (Chiroscience), L-748731 (Merck), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), prodrugs of any of them, and mixtures thereof.

[000142] More preferred is that the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

[000143] Even more preferred still is that the Cox-2 selective inhibitor is celecoxib.

5       **[000144]** Various classes of Cox-2 inhibitors useful in the present invention can be prepared as follows. Pyrazoles can be prepared by methods described in WO 95/15316. Pyrazoles can further be prepared by methods described in WO 95/15315. Pyrazoles can also be prepared by methods described in WO 96/03385.

10       **[000145]** Thiophene analogs useful in the present invention can be prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932.

**[000146]** Oxazoles useful in the present invention can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980.

15       **[000147]** Isoxazoles useful in the present invention can be prepared by the methods described in WO 96/25405.

**[000148]** Imidazoles useful in the present invention can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387.

20       **[000149]** Cyclopentene Cox-2 inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentene Cox-2 inhibitors is also described in WO 95/00501.

**[000150]** Terphenyl compounds useful in the present invention can be prepared by the methods described in WO 96/16934.

25       **[000151]** Thiazole compounds useful in the present invention can be prepared by the methods described in WO 96/03,392.

**[000152]** Pyridine compounds useful in the present invention can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585.

30       **[000153]** Benzopyranopyrazolyl compounds useful in the present invention can be prepared by the methods described in WO 96/09304.



5      **[000154]** Chromene compounds useful in the present invention can be prepared by the methods described in WO 98/47890. Preparation of chromene compounds is also described in WO 00/23433. Chromene compounds can further be prepared by the methods described in U.S. Patent No. 6,077,850. Preparation of chromene compounds is further described in U.S. Patent No. 6,034,256.

10      **[000155]** Arylpyridazinones useful in the present invention can be prepared by the methods described in WO 00/24719. Preparation of arylpyridazinones is also described in WO 99/10332. Arylpyridazinones can further be prepared by the methods described in WO 99/10331.

**[000156]** 5-Alkyl-2-arylaminophenylacetic acids and derivatives useful in the present invention can be prepared by the methods described in WO 99/11605.

15      **[000157]** Diarylmethylidenefuran derivative Cox-2 selective inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 6,180,651.

**[000158]** The celecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

20      **[000159]** The valdecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

25      **[000160]** The parecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

**[000161]** The rofecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,474,995.

30      **[000162]** The deracoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

[000163] The etoricoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 98/03484.

5 [000164] The meloxicam used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,233,299.

10 [000165] The compound 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,994,381.

[000166] The compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 00/24719.

15 [000167] The compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one used in the compositions and methods of the present invention can be prepared in the manner set forth in EP 863134.

20 [000168] The compound 2-[(2-chloro-6-fluorophenyl)amino]-5-methylbenzeneacetic acid used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 99/11605.

25 [000169] The compound N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,885,367.

[000170] The compound (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 6,180,651.

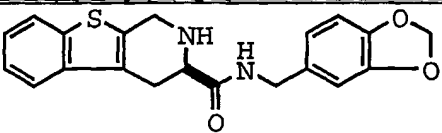
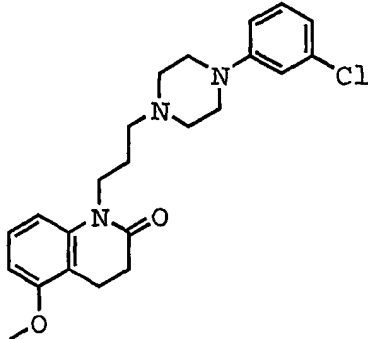
30 [000171] Another element of the present invention is a 5-HT<sub>1A</sub> receptor modulator. The expression "5-HT<sub>1A</sub> receptor" refers to the 5-

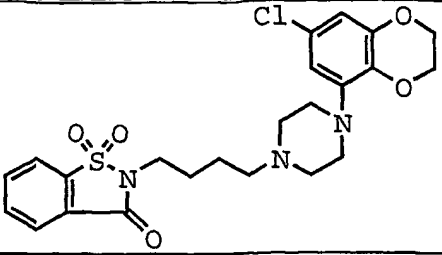
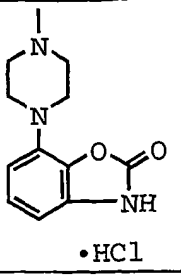
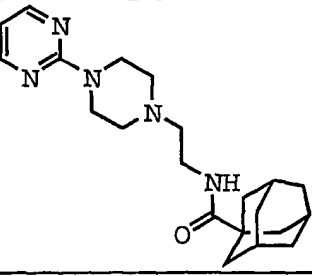
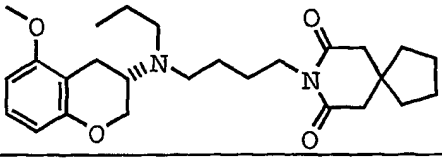
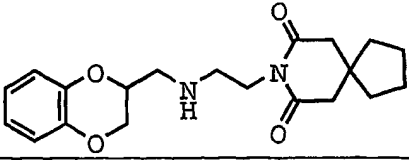
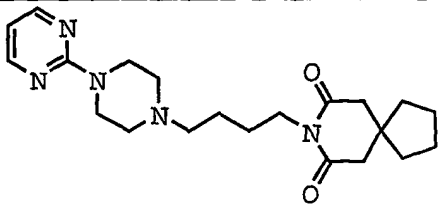
hydroxytryptamine<sub>1A</sub> receptor, which is pharmacologically characterized by its high affinity for 5-hydroxytryptamine (5-HT, serotonin). The expression "5-HT<sub>1A</sub> receptor" refers to proteins having amino acid sequences which are substantially similar to native mammalian 5-hydroxytryptamine<sub>1A</sub> receptors or 5-hydroxytryptamine<sub>1A</sub> amino acid sequences, and which are capable of binding 5-hydroxytryptamine molecules and inhibiting 5-hydroxytryptamine from binding to the 5-hydroxytryptamine<sub>1A</sub> receptor. The human 5-HT<sub>1A</sub> receptor is located on chromosome 5q11.2-q13 and has 422 amino acids.

**[000172]** The expression "5-HT<sub>1A</sub> receptor modulator" refers to a compound that binds to the 5-HT<sub>1A</sub> receptor and modulates its activity, with, for example, agonist, reverse agonist, antagonist or mixed effects.

**[000173]** The structures of some examples of preferred 5-HT<sub>1A</sub> receptor modulators are listed in Table No. 3 below.

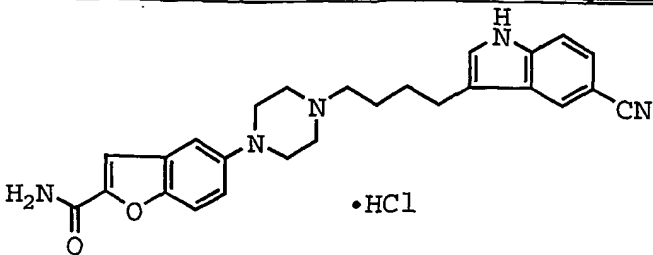
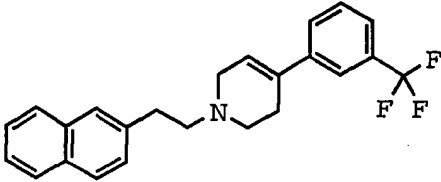
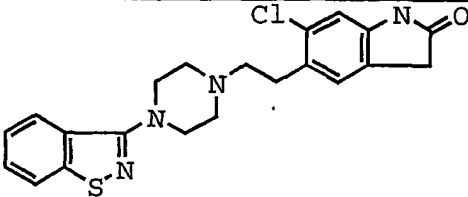
Table 3. Examples of 5-HT<sub>1A</sub> Receptor Modulators

| Compound Number | Structure  |
|-----------------|--|
| H1              |  |
| H2              |  |

| Compound Number | Structure  |
|-----------------|--|
| H3              |          |
| H4              | <br>•HCl |
| H5              |         |
| H6              |        |
| H7              |        |
| H8              |        |

| Compound Number | Structure |
|-----------------|-----------|
| H10             |           |
| H11             |           |
| H12             |           |
| H13             |           |
| H14             |           |
| H15             |           |

| Compound Number | Structure    |
|-----------------|--------------|
| H16             | <p>•3HCl</p> |
| H17             | <p>•HCl</p>  |
| H18             | <p>•HCl</p>  |
| H19             | <p>•HCl</p>  |
| H20             | <p>•HCl</p>  |
| H22             | <p>•HCl</p>  |
| H23             | <p>•HCl</p>  |

| Compound Number | Structure  |
|-----------------|--|
| H24             | <br><chem>Nc1cc2c(c1)oc3ccc(cc23)N4CCN(CC4)CCCC5=CNC6=CC=CC=C5C#N.Cl</chem>        |
| H26             | <br><chem>C1=CC=C2C(=C1)C(=CC=C2)CCN3CCN(CC3)CC4=CC=C(C(F)(F)F)C=C4</chem>         |
| H27             | <br><chem>Clc1cc2c(c1)nc(=O)[nH]2CCN3CCN(CC3)CC4=CC=C5C(=N4)S=C6C=CC=CC=C65</chem> |

[000174] The names, CAS registry numbers and references for examples of preferred 5-HT<sub>1A</sub> receptor modulators are listed in Table.4, below.

Table 4. Examples of preferred 5-HT<sub>1A</sub> Receptor Modulator Names, CAS Registry Numbers and References

| Compound Number | Name(s)  | CAS Registry Number | Reference      |
|-----------------|--|---------------------|----------------|
| H1              | (R)-N-(1,3-benzodioxol-5-ylmethyl)-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine-3-carboxamide, (AP-521)                    | 151227-58-6         | JP07109281     |
| H2              | 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1H)-quinolinone (OPC-14523)                             | 145969-30-8         | EP512525       |
| H3              | 2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2H)-one, 1,1-dioxide (DU-125530) | 161611-99-0         |                |
| H4              | 7-(4-methyl-1-piperazinyl)-2(3H)benzoxazolone, monohydrochloride (SLV-308)   | 269718-83-4         | WO0029397      |
| H5              | adatanserin  | 127266-56-2         | US5010078      |
| H6              | alnespirone  | 138298-79-0         | EP452204       |
| H7              | binospirone  | 102908-59-8         | EP170213       |
| H8              | buspirone  | 36505-84-7          | US3717634      |
| H9              | DU-127090  | 362524-71-8         |                |
| H10             | 2-[1-[1-[2-(2-fluorophenyl)ethyl]piperidino-4-yl]-1H-indol-6-yl]-N-methylacetamide (E-2101)                                    |                     | WO9843956      |
| H11             | eptapirone   | 179756-85-5         | WO0961694<br>9 |
| H12             | flibanserin  | 167933-07-5         | EP526434       |
| H13             | gepirone   | 83928-76-1          | US4423049      |
| H14             | ipsapirone   | 95847-70-4          | DE3321969      |
| H15             | lesopitron   | 132449-46-8         | EP382637       |
| H16             | N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamide, trihydrochloride (WAY-100635)             | 146714-97-8         | EP512755       |
| H17             | N-[3-(1,3-benzodioxol-5-   | 137275-80-0         | EP452204       |



| Compound Number | Name(s)   | CAS Registry Number | Reference      |
|-----------------|---|---------------------|----------------|
|                 | yl oxy)propyl]-2,3-dihydro-(2S)-1,4-benzodioxin-2-methanamine, hydrochloride (MKC-242)  |                     |                |
| H18             | repinotan (BAY X3702)   | 144980-29-0         | EP749970       |
| H19             | robalzotan  | 169758-66-1         | WO0951189<br>1 |
| H20             | sarizotan   | 177975-08-5         | EP707007       |
| H21             | SLV-319   |                     |                |
| H22             | SUN-N4057   | 182415-09-4         | WO9624594      |
| H23             | tandospirone  | 87760-53-0          | EP82402        |
| H24             | vilazodone  | 163521-08-2         | EP648767       |
| H25             | VML-670   |                     |                |
| H26             | xaliproden  | 135354-02-8         | EP101381       |
| H27             | ziprasidone   | 146939-27-7         | US4883795      |
| H28             | 6-hydroxy-buspirone   |                     | US6150365      |
| H29             | pyrazolidine derivative   |                     | EP736526       |
| H30             | Heteroaryloxyethylamines  |                     | US6063784      |
| H31             | 5-hydroxytryptamine, 5-methoxytryptamine, buspirone, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), ipsaspirone, gepirone, SM23997, lysergic acid, diethylamide, and agonistic antibodies |                     | WO9210200      |
| H32             | piperazine derivatives  |                     | WO9311122      |
| H33             | 8-(2-aminoalkoxy) fluorochroman derivative  |                     | WO9429293      |
| H34             | abeo-ergoline derivatives   |                     | WO9528403      |
| H35             | A-74283   | 131818-91-2         |                |
| H36             | AP-159  | 129592-83-2         |                |
| H37             | AZ 16596  | 257864-15-6         |                |
| H38             | 2- [[4-(2-Methoxyphenyl)piperazin-1-yl] methyl] octahydroimidazo [1,5-a] pyridine-1,3-dione (B 20991)   |                     |                |
| H39             | BMS 181100 (BMY 14802)  | 105565-56-8         |                |
| H40             | BMS 181101 (BMY 42569)  | 146479-45-0         | DE03507983     |
| H41             | BMS 181970  |                     |                |
| H42             | 1-methyl-4- [7-(4-chlorophenyl)methylaminocarbonyl]   |                     |                |

| Compound Number | Name(s)   | CAS Registry Number        | Reference  |
|-----------------|---|----------------------------|------------|
|                 | naphthyl-piperazine (CP291952)  |                            |            |
| H43             | (omega-piperazinylalkoxy)alkylenedioxybenzene (BP 554)                                    |                            | JP57080379 |
| H44             | E 5165  |                            |            |
| H45             | E 6265  |                            |            |
| H46             | Ebalzotan   | 149494-37-1                |            |
| H47             | Eltoprazine   | 98224-03-4                 |            |
| H48             | F 11440   | 179756-58-2                |            |
| H49             | F 13714   |                            |            |
| H50             | Flesinoxan  |                            | EP00138280 |
| H51             | 2- [4-(3-Phenylpyrrolidin-1-yl)butyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (LB 50016) |                            |            |
| H52             | LY 41   | 140221-50-7                |            |
| H53             | (+/-)-4-Substituted-amino-6-substituted-1,3,4,5-tetrahydrobenz[c,d]indoles (LY 228729)    | 115994-79-0                | EP00153083 |
| H54             | LY 228730   |                            |            |
| H55             | LY 274600   | 132873-35-9                |            |
| H56             | LY 274601   | 132873-34-8                |            |
| H57             | LY 293284   | 141318-62-9                |            |
| H58             | 6-Heterocyclyl-4-amino-1,3,4,5-tetrahydrobenz CD indoles (LY 297996)                      | 156896-33-2                | EP00590971 |
| H59             | Isoxazole derivatives (LY 315535)   |                            | US5434174  |
| H60             | hetero-oxy alkanamines (LY 333068)  |                            | EP00722941 |
| H61             | LY 426965   | 326821-27-6                |            |
| H62             | LY 433221   |                            |            |
| H63             | MDL 72832   | 113777-33-6                |            |
| H64             | MDL 73975   | 159650-30-3                |            |
| H65             | NDL 249   | 169758-71-8<br>184675-01-2 |            |
| H66             | Nerisopam   | 102771-12-0                |            |
| H67             | Org 1301  | 142494-12-0                |            |
| H68             | 2-(2-oxo-hexahydropyrimidin-1-yl)propylaminomethyl-benzopyran (R 137696)                  |                            |            |

| Compound Number | Name(s)   | CAS Registry Number                       | Reference  |
|-----------------|---|---|------------|
| H69             | RU 24969  | 66611-26-5<br>107008-28-6                 |            |
| H70             | 1-[[5-[[4-substituted-1-piperazinyl]methyl]-pyrrol-2-yl or furan-2-yl]methyl-2-piperidinones (RWJ 25730)                |   | US4992441  |
| H71             | S 14489   | 153607-44-4                               |            |
| H72             | 1-Naphthyl-piperazine derivatives (S 14506)   | 135721-98-1                               | EP00434561 |
| H73             | 1-Naphthyl-piperazine derivatives (S 14671)   | 135722-27-9                               | EP00434561 |
| H74             | S 15535   | 146998-34-7                               |            |
| H75             | S 15931   | 153607-45-5                               |            |
| H76             | 8- [4- [N-(5-Acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)-Npropylamino] butyl] -8-azaspiro [4.5] decane-7,9-dione (S 23751) |   |            |
| H77             | SDZ 216-525   | 141533-35-9                               |            |
| H78             | SEP 109235  |   |            |
| H79             | SR 59026  |   |            |
| H80             | Sunepitron  | 131744-27-9                               |            |
| H81             | UH 301  | 127126-21-0<br>135308-68-8<br>187593-75-5 |            |
| H82             | WAY 100135  | 133025-23-7                               |            |
| H83             | WAY 100802  |   |            |
| H84             | Zalospirone   |   | GB02181731 |

[000175] Also useful as a 5-HT<sub>1A</sub> receptor modulator in the present invention is [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-[(5-methyl-pyridin-2-ylmethyl)amino]-methyl]piperidin-1-yl]-methadone] (F 13640), as described in Colpaert, F. C. *et al*, *Neuropharmacology*, 43:945-958 (2002).

[000176] Especially preferred 5-HT<sub>1A</sub> receptor modulators for the present invention include buspirone, gepirone, repinotan, tandospirone, xaliproden and ziprasidone.

[000177] The compounds useful in the present invention optionally can have no asymmetric carbon atoms, or, alternatively, the useful compounds can have one or more asymmetric carbon atoms. When the

useful compounds have one or more asymmetric carbon atoms, they therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting  
5 enantiomeric starting materials, or by separating isomers of compounds of the present invention.

**[000178]** Isomers may include geometric isomers, for example cis-isomers or trans-isomers across a double bond. All such isomers are contemplated among the compounds useful in the present invention.

10 **[000179]** Also included in the methods, combinations and compositions of the present invention are the isomeric forms and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric,  
15 ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric  
20 and galacturonic acids.

**[000180]** Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa)  
25 salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chlorprocaine, choline,  
30 diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art

by conventional means from the corresponding compound of the present invention.

5 [000181] Also included in the methods, combinations and compositions of the present invention are the prodrugs of the described compounds and the pharmaceutically-acceptable salts thereof. The term "prodrug" refers to drug precursor compounds which, following administration to a subject and subsequent absorption, are converted to an active species *in vivo* via some process, such as a metabolic process. Other products from the conversion process are easily disposed of by the body. More preferred  
10 prodrugs produce products from the conversion process that are generally accepted as safe. A nonlimiting example of a "prodrug" that will be useful in the methods, combinations and compositions of the present invention is parecoxib (N-[[4-(5-methyl-3-phenyl-4-isoxazoly)]phenyl]sulfonyl]propanamide), which is a prodrug for  
15 valdecoxib.

[000182] The methods and combinations of the present invention are useful for the treatment or prevention of pain, inflammation, or inflammation-related disorder. In a preferred embodiment, the subject is one that is in need of treatment or prevention of pain, inflammation, or an  
20 inflammation-related disorder.

[000183] The methods and combinations of the present invention are also useful for the treatment or prevention of neurologic disease involving neurodegeneration.

25 [000184] The phrase "combination therapy" (or "co-therapy") embraces the administration of a Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic  
30 agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours,

days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single dosage form, such as a capsule, for example, having a fixed ratio of each therapeutic agent or in multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies.

[000185] The phrase "therapeutically effective" is intended to qualify the amount of compounds utilized in the therapy. This amount will achieve the goal of treating or preventing pain, inflammation or an inflammation-related disorder.

**[000186]** "Therapeutic compound" means a compound useful in the treatment or prevention of pain, inflammation or an inflammation-related disorder, or of a neurologic disorder involving neurodegeneration.

**[000187]** The term "pharmaceutically acceptable" is used adjectivally  
5 herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include  
10 aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-  
15 methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic  
20 acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

**[000188]** The term "comprising" means "including the following elements but not excluding others."

Combinations and Methods:

**[000189]** Among its several embodiments, the present invention provides  
25 a composition comprising Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator. It is preferred that the composition provides an amount of the Cox-2 inhibitor and an amount of the 5-HT<sub>1A</sub> receptor modulator wherein the amount of the Cox-2 inhibitor and the amount of the 5-HT<sub>1A</sub> receptor  
30 modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation, or an inflammation-related

disorder, and for the treatment or prevention of a neurologic disorder involving neurodegeneration.

**[000190]** In one embodiment, the Cox-2 inhibitor compound is a non-steroidal anti-inflammatory drug.

5 **[000191]** In another embodiment, the Cox-2 inhibitor is a Cox-2 selective inhibitor.

**[000192]** In still another embodiment, the the Cox-2 inhibitor compound is a prodrug of a Cox-2 inhibitor compound, illustrated herein with parecoxib.

10 **[000193]** In yet another embodiment, the present invention further provides a combination therapy method for the treatment or prevention of pain, inflammation, or an inflammation-related disorder in a mammal in need thereof, comprising administering to the mammal an amount of a Cox-2 inhibitor and an amount of a 5-HT<sub>1A</sub> receptor modulator wherein the  
15 amount of the Cox-2 inhibitor and the amount of the 5-HT<sub>1A</sub> receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation, or an inflammation-related disorder.

**[000194]** In a further embodiment, the present invention provides a  
20 pharmaceutical composition for the treatment or prevention of pain, inflammation, or an inflammation-related disorder comprising an amount of a Cox-2 inhibitor and an amount of a 5-HT<sub>1A</sub> receptor modulator and a pharmaceutically-acceptable excipient.

**[000195]** In still further embodiment, the present invention provides a kit  
25 that is suitable for use in the treatment, prevention or inhibition of pain, inflammation, or an inflammation-related disorder wherein the kit comprises a first dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a 5-HT<sub>1A</sub> receptor modulator, in quantities which  
30 comprise a therapeutically effective amount of the compounds for the treatment, prevention or inhibition of pain, inflammation, or an inflammation-related disorder.



[000196] The methods and compositions of the present invention provide one or more benefits. Combinations of Cox-2 inhibitors and 5-HT<sub>1A</sub> receptor modulators are useful in treating and preventing pain, inflammation, or an inflammation-related disorder. Preferably, the Cox-2 inhibitors and the 5-HT<sub>1A</sub> receptor modulators of the present invention are administered in combination at a low dose, that is, at a dose lower than has been conventionally used in clinical situations.

[000197] The combinations of the present invention will have a number of uses. For example, through dosage adjustment and medical monitoring, the individual dosages of the therapeutic compounds used in the combinations of the present invention will be lower than are typical for dosages of the therapeutic compounds when used in monotherapy. The dosage lowering will provide advantages including reduction of side effects of the individual therapeutic compounds when compared to the monotherapy. In addition, fewer side effects of the combination therapy compared with the monotherapies will lead to greater subject compliance with therapy regimens.

[000198] Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at higher doses.

[000199] When administered as a combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

[000200] Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid that are used in the treatment, prevention or reduction of pain, inflammation, or an inflammation-related disorder may inhibit enzyme activity through a variety of mechanisms. By way of example, the cyclooxygenase-2 inhibitors used in the methods described herein may block the enzyme activity directly by binding at the substrate site of the enzyme. The use of a Cox-2 selective inhibiting agent is highly advantageous in that it minimizes the gastric side effects that can occur

with non-selective non-steroidal antiinflammatory drugs (NSAIDs), especially where prolonged treatment is expected.

5 [000201] Besides being useful for human treatment, these methods are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, avians, and the like. More preferred animals include horses, dogs, and cats.

[000202] As used herein, the terms "therapeutically effective amount" are intended to qualify the amount of a Cox-2 inhibiting agent and a 5-HT<sub>1A</sub> receptor modulator that are required to treat or prevent pain, inflammation, or an inflammation-related disorder, or to treat or prevent neurologic disease involving neurodegeneration.

10

[000203] The combinations and methods of the present invention would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-related disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

15

[000204] Such combinations and methods of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, overactive bladder (OAB), preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, UV damage, burns and dermatitis, and postoperative inflammation including ophthalmic surgery such as cataract surgery and refractive surgery.

20

25

[000205] Combinations and methods of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

30

5       **[000206]** Combinations and methods of the invention would be useful in treating inflammation in such diseases as migraine headaches, polyarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

10       **[000207]** The combinations and methods of the invention would also be useful in the treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, glaucoma and acute injury to the eye tissue.

15       **[000208]** The combinations and methods would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as associated with osteoporosis.

20       **[000209]** The combinations and methods of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These combinations and methods would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and liver disease.

25       **[000210]** The combinations and methods would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, dysmennorrhea, neuropathic pain and pain resulting from cancer.

30       **[000211]** The combinations and methods above would be useful for, but not limited to, treating and preventing inflammation-related cardiovascular disorders in a subject. The combinations and methods would be useful for treatment and prevention of vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke

(hemorrhagic or ischemic), thrombosis, including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

[000212] The combinations and methods would be useful for, but not limited to, the treatment and prevention of angiogenesis-related disorders in a subject. According to the present invention, the compounds can be administered to a subject in need of angiogenesis inhibition. The method would be useful for treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

[000213] Compounds of the invention would be useful for the prevention or treatment of benign and malignant tumors/neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Preferably, neoplasia is selected from gastrointestinal cancer,

Barrett's esophagus, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers. The compounds can also be used to treat the fibrosis which occurs with radiation therapy. The method can be used to treat subjects having adenomatous polyps, including those with sporadic adenomatous polyposis (SAP) or familial adenomatous polyposis (FAP). Additionally, the method can be used to prevent polyps from forming in subjects at risk of FAP.

[000214] The combinations and methods of the present invention are useful for the prevention and treatment of pain, inflammation and central nervous system (CNS) disorders, which include, for example, adjustment disorders, such as anxiety (mixed anxiety), mood (depressed), conduct disturbance, mixed anxiety and mood (conduct); addictive disorders, such as alcohol abuse, intoxication disorders, nicotine abuse, psychoactive substances abuse and substance disorder; withdrawal syndromes; acute trauma; age associated mental disorders, such as learning and Alzheimer's disease; agitation disorders, such as agitation in Alzheimer's disease and agitation in the elderly; aggressive behavior, such as in Alzheimers disease; amyloidosis, such as aging / senile, hereditary, immunocyte derived, lichen, primary, reactive systemic, secondary, senile (Alzheimer's disease), amyotrophy & amyotrophic lateral sclerosis (ALS), and anorexia nervosa; anxiety disorders, such as generalized anxiety disorder (GAD), panic disorder, bipolar disorder, social phobias and stress related diseases; apathy; attention deficit disorder (ADD); attention deficit hyperactivity disorder (ADHD); autism; auto immune disorders, such as lupus erythematosus and multiple sclerosis; behavioral disturbances, such as agitation plus diminished cognition, bipolar I disorder and bipolar II disorder; bulimia nervosa; cardiovascular; blood pressure modification, such as for hypertension, hypotension and heart rate modification; chemotherapy-induced vomiting; chronic fatigue immune disorders (CFIDS); chronic fatigue syndrome (CFS); cognitive dysfunction, such as

cortical dementias including mild cognitive impairment (MCI), Lewy Body dementia, vascular dementia, neurodegeneration, and cognitive dysfunction resulting from stroke, ischemia, trauma, or surgical procedures, including coronary artery bypass surgery; cognition  
5 enhancement; conduct disorder; cyclothymia; delusional disorder; depression, such as adolescent, in Alzheimer's disease, general, minor, in Parkinson's disease and diabetic neuropathy; dissociative disorders; developmental disorders, such as learning disabilities, language disorders and mental retardation; dementia, such as associated with aging, illness,  
10 neurodegeneration and dyskenia; dysthymia; dystonia; eating disorders, such as anorexia nervosa, bulimia nervosa, obesity, epilepsy and fibromyalgia syndrome (FMS); gastrointestinal disorders, such as irritable bowel syndrome, psychogenic effects and stress-related; growth retardation effects, such as endocrine, psychosocial and stress-related;  
15 heart rate modification; Huntington's Chorea; hypertension; immune system disorders, such as immune system depression; impulse control (related to conduct disorder); incontinence, such as mixed states, stress incontinence and urge incontinence; infectious neuropathy, such as AIDS; carpal tunnel syndrome; dementia; irritable bowel syndrome (IBS), such as  
20 constipative and diarrhea-predominant; inflammatory bowel disease (IBD), such as constipation-predominant, diarrhea-predominant and mixed states; inhalation disorder; lactation inhibition, metabolic & chromosomal disorders, such as galactosemia phenylketonuria, fatty acid disorder, infantile nephropathic cystinosis, orthithrotranscarbamylase porphyria and  
25 migraine; mood disorders, such as atypical depression, bipolar disorder (including psychotic features), major depressive disorder, mania, and seasonal affective disorder; movement disorders, such as athetosis, chorea, dyskinesia, dystonia, restless leg syndrome (RLS), tremor plus periodic limb movement (PLM), periodic limb movements of sleep (PLMS),  
30 Huntington's chorea, Parkinson's disease, PLM, PLMS, progressive supranuclear palsy, stereotypy (various), torticollis, tic disorders and tremor; multisystemic atrophy (MSA), such as multiple sclerosis;

neuroendocrine system disorders; neurologic diseases involving neurodegeneration, such as amyotrophy, amyotrophy diabetics, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Huntington's chorea and Parkinson's disease; neurological disorders; neuropathy, such as diabetic and peripheral; neuroprotective effects, such as for ischemic brain injury, myocardial infarction, spinal cord injury, traumatic brain injury and obesity; obsessive compulsive disorder (OCD); oncology related disorders, such as with behavior abnormalities resulting from tumors or treatments, such as chemotherapy and induced vomiting; oppositional defiant disorder; pain disorders, such as acute, chronic, cluster headache, dysmenorrhea, labor, migraine, neuropathic, AIDs-related, cancer-related, chemotherapeutic-induced, diabetic, post-herpetic neuralgia, radiation-induced, osteoarthritis flare, phantom limb, surgical, post-surgical and incisional, psychic, regional pain (such as abdominal region, chronic back pain, complex-regional pain disorder, dental, face and mouth, head, lower back and peripheral), rheumatoid arthritis, starting pain and systematic pain (such as in connective tissue, such as musculoskeletal, nervous system, urogenital, uterine contractions); panic disorder, such as with agoraphobia and without agoraphobia; Parkinson's disease; peripheral neuropathy; personality disorders; phobias (simple), such as phobias of animals, closed spaces (claustrophobia), heights (acrophobia), public places (agoraphobia); phobias (Social), such as, public eating, public embarrassment, public performance / speaking and using public lavatories; SSRI poop out syndrome; post-traumatic stress disorder; progressive supranuclear palsy (PSP); prolactin plasma level disorders; psychotic disorders, such as brief and long duration, due to medical condition, not otherwise specified (NOS) and restless leg syndrome (RLS); schizophrenias, such as delusional (paranoid) disorder, schizoaffective disorders, schizophreniform disorders and seasonal affective disorder; seizure disorders, such as epilepsy (partial) and epilepsy (generalized); sexual dysfunction, such as for female and for male; sleep disorders, such as apnea, parasomnias, insomnia, narcolepsy, obstructive, and disorders

of circadian rhythm, enuresis, initiation and maintenance; social phobias, such as social anxiety disorder; somatoform disorders, such as conversion, body, dysmorphic, fibromyalgia syndrome (FMS), hypochondriasis, NOS, somatization and undifferentiated; specific  
5 developmental disorders; stress disorders, such as acute, chronic and incontinence; spectrum disorders; stroke; suicidal behavior, and in particular, prevention of and amelioration of; thyroid stimulating hormone disorders (TSH); Tourette's syndrome; tooth-germ morphogenesis disorders; thermoregulation disorders; TSH modulating agent disorders; tic  
10 disorders; trauma, such as acute head, and related effects, such as blood pressure regulation, cerebral blood flow, CSF production, inflammation, and ischemia; vasospasms; vasoreactive headaches and violent behavior.  
[000215] As used herein, the term "treatment" includes partial or total inhibition of the dementia or cognitive dysfunction, including Alzheimer's  
15 disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, and senile dementia.  
[000216] The combinations and methods of the present invention are particularly useful for the treatment, prevention or inhibition of a central nervous system disorder associated with stroke (ischemic or  
20 hemorrhagic) or other ischemic brain injury.  
[000217] The phrases "low dose" or "low dose amount", in characterizing a therapeutically effective amount of the Cox-2 selective inhibitor and the 5-HT<sub>1A</sub> receptor modulator or therapy in the combination therapy, defines  
25 a quantity of such agent, or a range of quantity of such agent, that is capable of reducing the discomfort of pain, inflammation, or an inflammation-related disorder while optionally reducing or avoiding one or more side effects of monotherapy with a 5-HT<sub>1A</sub> receptor modulator or other pain-relieving agent. Side effects of 5-HT<sub>1A</sub> receptor modulators that  
30 the selected combinations of the present invention may reduce or avoid are nausea, dizziness, insomnia, headache, fatigue, paresthesias, uneasiness, nervousness, lightheadedness, excitement, tachycardia,



malaise, dysphoria, dry mouth, headache, somnolence, constipation, abnormal movements, respiratory disorders, dyspepsia, skin rash, elevations in liver enzymes and gastrointestinal disturbances.

5 [000218] The phrase "adjunctive therapy" encompasses treatment of a subject with agents that reduce or avoid side effects associated with the combination therapy of the present invention.

Dosages, Formulations and Routes of Administration:

10 [000219] Dosage levels of the Cox-2 inhibiting agent (*e.g.*, a Cox-2 selective inhibiting agent or a prodrug of a Cox-2 selective inhibiting agent) on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 1.0 mg to about 1,000 mg. While the dosage of active compound administered to a warm-blooded animal (a mammal), is dependent on the species of that mammal, the body weight, age, and individual condition, and on the route of administration, the unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 500 mg of the active ingredient (for example, Cox-189). The amount of active ingredient that may be combined with a 5-HT<sub>1A</sub> receptor modulator to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

20 [000220] A total daily dose of a 5-HT<sub>1A</sub> receptor modulator can generally be in the range of from about 0.001 to about 10,000 mg/day in single or divided doses, with preferred levels of about 1.0 mg to about 1,000 mg. It is understood, however, that specific dose levels of the therapeutic agents or therapeutic approaches of the present invention for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the drug combination, and the severity of the particular disease being treated and form of administration.

25

30

[000221] Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from *in vitro* initially can provide useful guidance on the proper doses for subject administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of pain, inflammation, or an inflammation-related disorder in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular subject, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective *in vitro*. Thus, where a compound is found to demonstrate *in vitro* activity at, e.g., 10  $\mu$ M, one will desire to administer an amount of the drug that is effective to provide about a 10  $\mu$ M concentration *in vivo*. Determination of these parameters is well within the skill of the art.

[000222] Effective formulations and administration procedures are well known in the art and are described in standard textbooks.

[000223] The Cox-2 inhibiting agents or the 5-HT<sub>1A</sub> receptor modulators can be formulated as a single pharmaceutical composition or as independent multiple pharmaceutical compositions. Pharmaceutical compositions according to the present invention include those suitable for oral, inhalation spray, rectal, topical, buccal (e.g., sublingual), or parenteral (e.g., subcutaneous, intramuscular, intravenous, intrathecal, intramedullary and intradermal injections, or infusion techniques) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral or parenteral.

[000224] Compounds and composition of the present invention can then be administered orally, by inhalation spray, rectally, topically, buccally or

parenterally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The compounds of the present invention can be administered by any conventional means available for use in conjunction with pharmaceuticals,  
5 either as individual therapeutic compounds or as a combination of therapeutic compounds.

**[000225]** Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically  
10 acceptable anion or cation.

**[000226]** The compounds useful in the methods, combinations and compositions of the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible  
15 with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be  
20 present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well-known techniques of pharmacy, consisting essentially of admixing the components.

**[000227]** The amount of compound in combination that is required to achieve the desired biological effect will, of course, depend on a number  
25 of factors such as the specific compound chosen, the use for which it is intended, the mode of administration, and the clinical condition of the recipient.

**[000228]** The compounds of the present invention can be delivered orally  
30 either in a solid, in a semi-solid, or in a liquid form. Dosing for oral administration may be with a regimen calling for single daily dose, or for a single dose every other day, or for multiple, spaced doses throughout the

day. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid.

Capsules, tablets, etc., can be prepared by conventional methods well known in the art. The pharmaceutical composition is preferably made in

5 the form of a dosage unit containing a particular amount of the active ingredient or ingredients. Examples of dosage units are tablets or capsules, and may contain one or more therapeutic compounds in an amount described herein. For example, in the case of a 5-HT<sub>1A</sub> receptor modulator, the dose range may be from about 0.01 mg to about 5,000 mg  
10 or any other dose, dependent upon the specific inhibitor, as is known in the art. When in a liquid or in a semi-solid form, the combinations of the present invention can, for example, be in the form of a liquid, syrup, or contained in a gel capsule (e.g., a gel cap). In one embodiment, when a 5-HT<sub>1A</sub> receptor modulator is used in a combination of the present  
15 invention, the 5-HT<sub>1A</sub> receptor modulator can be provided in the form of a liquid, syrup, or contained in a gel capsule. In another embodiment, when a Cox-2 inhibiting agent is used in a combination of the present invention, the Cox-2 inhibiting agent can be provided in the form of a liquid, syrup, or contained in a gel capsule.

20 [000229] Oral delivery of the combinations of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine,  
25 slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. For some of the therapeutic compounds useful in the methods, combinations and compositions of the present  
30 invention the intended effect is to extend the time period over which the active drug molecule is delivered to the site of action by manipulation of

the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention.

Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

5 **[000230]** Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one therapeutic compound useful in the present invention; as a powder or  
10 granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can constitute one or more accessory ingredients). In  
15 general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients.

20 Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with  
25 an inert liquid diluent.

**[000231]** Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as  
30 water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

5       **[000232]** Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

10       **[000233]** Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection or by infusion. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 10% w/w of a compound disclosed  
15       herein.

20       **[000234]** Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this  
25       purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

30       **[000235]** The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. A suitable daily dose of each active therapeutic compound is one that achieves the same blood serum level as produced by oral administration as described above.

5       **[000236]** The dose of any of these therapeutic compounds can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 10,000 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampules for injection can contain, for example, from about 1 mg to about 100 mg.

10       **[000237]** Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound or compounds of the present invention with one or more conventional solid carriers, for example, cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug; and then  
15       shaping the resulting mixture.

**[000238]** Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include petroleum jelly  
20       (e.g., Vaseline), lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound or compounds are generally present at a concentration of from 0.1 to 50% w/w of the composition, for example, from 0.5 to 2%.

**[000239]** Transdermal administration is also possible. Pharmaceutical  
25       compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound or compounds of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an  
30       adhesive, or dispersed in a polymer. A suitable concentration of the active compound or compounds is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound or compounds can be

delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

5 [000240] In any case, the amount of active ingredients that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

10 [000241] In combination therapy, administration of two or more of the therapeutic agents useful in the methods, combinations and compositions of the present invention may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or in a separate formulation. Independent administration of each therapeutic agent may be accomplished by, for example, oral, inhalation spray, rectal, topical, buccal (*e.g.*, sublingual), or parenteral (*e.g.*, subcutaneous, intramuscular, intravenous, intrathecal, 15 intramedullary and intradermal injections, or infusion techniques) administration. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. Solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable 20 carriers or diluents, or a binder such as gelatin or hydroxypropylmethyl cellulose, together with one or more of a lubricant, preservative, surface active or dispersing agent. The therapeutic compounds may further be administered by any combination of, for example, oral/oral, oral/parenteral, or parenteral/parenteral route.

25 [000242] The therapeutic compounds which make up the combination therapy may be a combined dosage form or in separate dosage forms intended for substantially simultaneous oral administration. The therapeutic compounds which make up the combination therapy may also be administered sequentially, with either therapeutic compound being 30 administered by a regimen calling for two step ingestion. Thus, a regimen may call for sequential administration of the therapeutic compounds with spaced-apart ingestion of the separate, active agents. The time period



between the multiple ingestion steps may range from, for example, a few minutes to several hours to days, depending upon the properties of each therapeutic compound such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the therapeutic compound, as well as

5 depending upon the effect of food ingestion and the age and condition of the subject. Circadian variation of the target molecule concentration may also determine the optimal dose interval. The therapeutic compounds of the combined therapy whether administered simultaneously, substantially simultaneously, or sequentially, may involve a regimen calling for

10 administration of one therapeutic compound by oral route and another therapeutic compound by intravenous route. Whether the therapeutic compounds of the combined therapy are administered orally, by inhalation spray, rectally, topically, buccally (*e.g.*, sublingual), or parenterally (*e.g.*, subcutaneous, intramuscular, intravenous and intradermal injections, or

15 infusion techniques), separately or together, each such therapeutic compound will be contained in a suitable pharmaceutical formulation of pharmaceutically-acceptable excipients, diluents or other formulations components. Examples of suitable pharmaceutically-acceptable formulations containing the therapeutic compounds are given above.

20 Additionally, drug formulations are discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975. Another discussion of drug formulations can be found in Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

25 **[000243]** The following examples describe preferred embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, taken together with the examples, be considered to be

30 exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples, all percentages are given on a weight basis, unless otherwise indicated.

**EXAMPLE 1**

[000244] This example illustrates combinations of the present invention.

[000245] Table 5 describes a number of combinations comprising a Cox-2 selective inhibitor and a 5-HT<sub>1A</sub> receptor modulator. Designations of "H"

5 correspond to compounds described above in the specification.

**Table 5.** Combinations of Cox-2 selective inhibiting agents and 5-HT<sub>1A</sub> receptor modulators.

| <b>Example Number</b> | <b>Cox-2 Inhibitor</b> | <b>5-HT<sub>1A</sub> Receptor Modulator</b> |
|-----------------------|------------------------|---|
| 1                     | Celecoxib              | H1  |
| 2                     | Celecoxib              | H2  |
| 3                     | Celecoxib              | H3  |
| 4                     | Celecoxib              | H4  |
| 5                     | Celecoxib              | H5  |
| 6                     | Celecoxib              | H6  |
| 7                     | Celecoxib              | H7  |
| 8                     | Celecoxib              | H8  |
| 9                     | Celecoxib              | H9  |
| 10                    | Celecoxib              | H10   |
| 11                    | Celecoxib              | H11   |
| 12                    | Celecoxib              | H12   |
| 13                    | Celecoxib              | H13   |
| 14                    | Celecoxib              | H14   |
| 15                    | Celecoxib              | H15   |
| 16                    | Celecoxib              | H16   |
| 17                    | Celecoxib              | H17   |
| 18                    | Celecoxib              | H18   |
| 19                    | Celecoxib              | H19   |
| 20                    | Celecoxib              | H20   |
| 21                    | Celecoxib              | H21   |
| 22                    | Celecoxib              | H22   |
| 23                    | Celecoxib              | H23   |
| 24                    | Celecoxib              | H24   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 25             | Celecoxib       | H25                                   |
| 26             | Celecoxib       | H26                                   |
| 27             | Celecoxib       | H27                                   |
| 28             | Celecoxib       | H28                                   |
| 29             | Celecoxib       | H29                                   |
| 30             | Celecoxib       | H30                                   |
| 31             | Celecoxib       | H31                                   |
| 32             | Celecoxib       | H32                                   |
| 33             | Celecoxib       | H33                                   |
| 34             | Celecoxib       | H34                                   |
| 35             | Celecoxib       | H35                                   |
| 36             | Celecoxib       | H36                                   |
| 37             | Celecoxib       | H37                                   |
| 38             | Celecoxib       | H38                                   |
| 39             | Celecoxib       | H39                                   |
| 40             | Celecoxib       | H40                                   |
| 41             | Celecoxib       | H41                                   |
| 42             | Celecoxib       | H42                                   |
| 43             | Celecoxib       | H43                                   |
| 44             | Celecoxib       | H44                                   |
| 45             | Celecoxib       | H45                                   |
| 46             | Celecoxib       | H46                                   |
| 47             | Celecoxib       | H47                                   |
| 48             | Celecoxib       | H48                                   |
| 49             | Celecoxib       | H49                                   |
| 50             | Celecoxib       | H50                                   |
| 51             | Celecoxib       | H51                                   |
| 52             | Celecoxib       | H52                                   |
| 53             | Celecoxib       | H53                                   |
| 54             | Celecoxib       | H54                                   |
| 55             | Celecoxib       | H55                                   |
| 56             | Celecoxib       | H56                                   |
| 57             | Celecoxib       | H57                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 58             | Celecoxib       | H58                                   |
| 59             | Celecoxib       | H59                                   |
| 60             | Celecoxib       | H60                                   |
| 61             | Celecoxib       | H61                                   |
| 62             | Celecoxib       | H62                                   |
| 63             | Celecoxib       | H63                                   |
| 64             | Celecoxib       | H64                                   |
| 65             | Celecoxib       | H65                                   |
| 66             | Celecoxib       | H66                                   |
| 67             | Celecoxib       | H67                                   |
| 68             | Celecoxib       | H68                                   |
| 69             | Celecoxib       | H69                                   |
| 70             | Celecoxib       | H70                                   |
| 71             | Celecoxib       | H71                                   |
| 72             | Celecoxib       | H72                                   |
| 73             | Celecoxib       | H73                                   |
| 74             | Celecoxib       | H74                                   |
| 75             | Celecoxib       | H75                                   |
| 76             | Celecoxib       | H76                                   |
| 77             | Celecoxib       | H77                                   |
| 78             | Celecoxib       | H78                                   |
| 79             | Celecoxib       | H79                                   |
| 80             | Celecoxib       | H80                                   |
| 81             | Celecoxib       | H81                                   |
| 82             | Celecoxib       | H82                                   |
| 83             | Celecoxib       | H83                                   |
| 84             | Celecoxib       | H84                                   |
| 85             | Valdecoxib      | H1                                    |
| 86             | Valdecoxib      | H2                                    |
| 87             | Valdecoxib      | H3                                    |
| 88             | Valdecoxib      | H4                                    |
| 89             | Valdecoxib      | H5                                    |
| 90             | Valdecoxib      | H6                                    |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 91             | Valdecoxib      | H7                                    |
| 92             | Valdecoxib      | H8                                    |
| 93             | Valdecoxib      | H9                                    |
| 94             | Valdecoxib      | H10                                   |
| 95             | Valdecoxib      | H11                                   |
| 96             | Valdecoxib      | H12                                   |
| 97             | Valdecoxib      | H13                                   |
| 98             | Valdecoxib      | H14                                   |
| 99             | Valdecoxib      | H15                                   |
| 100            | Valdecoxib      | H16                                   |
| 101            | Valdecoxib      | H17                                   |
| 102            | Valdecoxib      | H18                                   |
| 103            | Valdecoxib      | H19                                   |
| 104            | Valdecoxib      | H20                                   |
| 105            | Valdecoxib      | H21                                   |
| 106            | Valdecoxib      | H22                                   |
| 107            | Valdecoxib      | H23                                   |
| 108            | Valdecoxib      | H24                                   |
| 109            | Valdecoxib      | H25                                   |
| 110            | Valdecoxib      | H26                                   |
| 111            | Valdecoxib      | H27                                   |
| 112            | Valdecoxib      | H28                                   |
| 113            | Valdecoxib      | H29                                   |
| 114            | Valdecoxib      | H30                                   |
| 115            | Valdecoxib      | H31                                   |
| 116            | Valdecoxib      | H32                                   |
| 117            | Valdecoxib      | H33                                   |
| 118            | Valdecoxib      | H34                                   |
| 119            | Valdecoxib      | H35                                   |
| 120            | Valdecoxib      | H36                                   |
| 121            | Valdecoxib      | H37                                   |
| 122            | Valdecoxib      | H38                                   |
| 123            | Valdecoxib      | H39                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 124            | Valdecoxib      | H40                                   |
| 125            | Valdecoxib      | H41                                   |
| 126            | Valdecoxib      | H42                                   |
| 127            | Valdecoxib      | H43                                   |
| 128            | Valdecoxib      | H44                                   |
| 129            | Valdecoxib      | H45                                   |
| 130            | Valdecoxib      | H46                                   |
| 131            | Valdecoxib      | H47                                   |
| 132            | Valdecoxib      | H48                                   |
| 133            | Valdecoxib      | H49                                   |
| 134            | Valdecoxib      | H50                                   |
| 135            | Valdecoxib      | H51                                   |
| 136            | Valdecoxib      | H52                                   |
| 137            | Valdecoxib      | H53                                   |
| 138            | Valdecoxib      | H54                                   |
| 139            | Valdecoxib      | H55                                   |
| 140            | Valdecoxib      | H56                                   |
| 141            | Valdecoxib      | H57                                   |
| 142            | Valdecoxib      | H58                                   |
| 143            | Valdecoxib      | H59                                   |
| 144            | Valdecoxib      | H60                                   |
| 145            | Valdecoxib      | H61                                   |
| 146            | Valdecoxib      | H62                                   |
| 147            | Valdecoxib      | H63                                   |
| 148            | Valdecoxib      | H64                                   |
| 149            | Valdecoxib      | H65                                   |
| 150            | Valdecoxib      | H66                                   |
| 151            | Valdecoxib      | H67                                   |
| 152            | Valdecoxib      | H68                                   |
| 153            | Valdecoxib      | H69                                   |
| 154            | Valdecoxib      | H70                                   |
| 155            | Valdecoxib      | H71                                   |
| 156            | Valdecoxib      | H72                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 157            | Valdecoxib      | H73                                   |
| 158            | Valdecoxib      | H74                                   |
| 159            | Valdecoxib      | H75                                   |
| 160            | Valdecoxib      | H76                                   |
| 161            | Valdecoxib      | H77                                   |
| 162            | Valdecoxib      | H78                                   |
| 163            | Valdecoxib      | H79                                   |
| 164            | Valdecoxib      | H80                                   |
| 165            | Valdecoxib      | H81                                   |
| 166            | Valdecoxib      | H82                                   |
| 167            | Valdecoxib      | H83                                   |
| 168            | Valdecoxib      | H84                                   |
| 169            | Parecoxib       | H1                                    |
| 170            | Parecoxib       | H2                                    |
| 171            | Parecoxib       | H3                                    |
| 172            | Parecoxib       | H4                                    |
| 173            | Parecoxib       | H5                                    |
| 174            | Parecoxib       | H6                                    |
| 175            | Parecoxib       | H7                                    |
| 176            | Parecoxib       | H8                                    |
| 177            | Parecoxib       | H9                                    |
| 178            | Parecoxib       | H10                                   |
| 179            | Parecoxib       | H11                                   |
| 180            | Parecoxib       | H12                                   |
| 181            | Parecoxib       | H13                                   |
| 182            | Parecoxib       | H14                                   |
| 183            | Parecoxib       | H15                                   |
| 184            | Parecoxib       | H16                                   |
| 185            | Parecoxib       | H17                                   |
| 186            | Parecoxib       | H18                                   |
| 187            | Parecoxib       | H19                                   |
| 188            | Parecoxib       | H20                                   |
| 189            | Parecoxib       | H21                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 190            | Parecoxib       | H22                                   |
| 191            | Parecoxib       | H23                                   |
| 192            | Parecoxib       | H24                                   |
| 193            | Parecoxib       | H25                                   |
| 194            | Parecoxib       | H26                                   |
| 195            | Parecoxib       | H27                                   |
| 196            | Parecoxib       | H28                                   |
| 197            | Parecoxib       | H29                                   |
| 198            | Parecoxib       | H30                                   |
| 199            | Parecoxib       | H31                                   |
| 200            | Parecoxib       | H32                                   |
| 201            | Parecoxib       | H33                                   |
| 202            | Parecoxib       | H34                                   |
| 203            | Parecoxib       | H35                                   |
| 204            | Parecoxib       | H36                                   |
| 205            | Parecoxib       | H37                                   |
| 206            | Parecoxib       | H38                                   |
| 207            | Parecoxib       | H39                                   |
| 208            | Parecoxib       | H40                                   |
| 209            | Parecoxib       | H41                                   |
| 210            | Parecoxib       | H42                                   |
| 211            | Parecoxib       | H43                                   |
| 212            | Parecoxib       | H44                                   |
| 213            | Parecoxib       | H45                                   |
| 214            | Parecoxib       | H46                                   |
| 215            | Parecoxib       | H47                                   |
| 216            | Parecoxib       | H48                                   |
| 217            | Parecoxib       | H49                                   |
| 218            | Parecoxib       | H50                                   |
| 219            | Parecoxib       | H51                                   |
| 220            | Parecoxib       | H52                                   |
| 221            | Parecoxib       | H53                                   |
| 222            | Parecoxib       | H54                                   |



| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 223            | Parecoxib       | H55                                   |
| 224            | Parecoxib       | H56                                   |
| 225            | Parecoxib       | H57                                   |
| 226            | Parecoxib       | H58                                   |
| 227            | Parecoxib       | H59                                   |
| 228            | Parecoxib       | H60                                   |
| 229            | Parecoxib       | H61                                   |
| 230            | Parecoxib       | H62                                   |
| 231            | Parecoxib       | H63                                   |
| 232            | Parecoxib       | H64                                   |
| 233            | Parecoxib       | H65                                   |
| 234            | Parecoxib       | H66                                   |
| 235            | Parecoxib       | H67                                   |
| 236            | Parecoxib       | H68                                   |
| 237            | Parecoxib       | H69                                   |
| 238            | Parecoxib       | H70                                   |
| 239            | Parecoxib       | H71                                   |
| 240            | Parecoxib       | H72                                   |
| 241            | Parecoxib       | H73                                   |
| 242            | Parecoxib       | H74                                   |
| 243            | Parecoxib       | H75                                   |
| 244            | Parecoxib       | H76                                   |
| 245            | Parecoxib       | H77                                   |
| 246            | Parecoxib       | H78                                   |
| 247            | Parecoxib       | H79                                   |
| 248            | Parecoxib       | H80                                   |
| 249            | Parecoxib       | H81                                   |
| 250            | Parecoxib       | H82                                   |
| 251            | Parecoxib       | H83                                   |
| 252            | Parecoxib       | H84                                   |
| 253            | Deracoxib       | H1                                    |
| 254            | Deracoxib       | H2                                    |
| 255            | Deracoxib       | H3                                    |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 256            | Deracoxib       | H4                                    |
| 257            | Deracoxib       | H5                                    |
| 258            | Deracoxib       | H6                                    |
| 259            | Deracoxib       | H7                                    |
| 260            | Deracoxib       | H8                                    |
| 261            | Deracoxib       | H9                                    |
| 262            | Deracoxib       | H10                                   |
| 263            | Deracoxib       | H11                                   |
| 264            | Deracoxib       | H12                                   |
| 265            | Deracoxib       | H13                                   |
| 266            | Deracoxib       | H14                                   |
| 267            | Deracoxib       | H15                                   |
| 268            | Deracoxib       | H16                                   |
| 269            | Deracoxib       | H17                                   |
| 270            | Deracoxib       | H18                                   |
| 271            | Deracoxib       | H19                                   |
| 272            | Deracoxib       | H20                                   |
| 273            | Deracoxib       | H21                                   |
| 274            | Deracoxib       | H22                                   |
| 275            | Deracoxib       | H23                                   |
| 276            | Deracoxib       | H24                                   |
| 277            | Deracoxib       | H25                                   |
| 278            | Deracoxib       | H26                                   |
| 279            | Deracoxib       | H27                                   |
| 280            | Deracoxib       | H28                                   |
| 281            | Deracoxib       | H29                                   |
| 282            | Deracoxib       | H30                                   |
| 283            | Deracoxib       | H31                                   |
| 284            | Deracoxib       | H32                                   |
| 285            | Deracoxib       | H33                                   |
| 286            | Deracoxib       | H34                                   |
| 287            | Deracoxib       | H35                                   |
| 288            | Deracoxib       | H36                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 289            | Deracoxib       | H37                                   |
| 290            | Deracoxib       | H38                                   |
| 291            | Deracoxib       | H39                                   |
| 292            | Deracoxib       | H40                                   |
| 293            | Deracoxib       | H41                                   |
| 294            | Deracoxib       | H42                                   |
| 295            | Deracoxib       | H43                                   |
| 296            | Deracoxib       | H44                                   |
| 297            | Deracoxib       | H45                                   |
| 298            | Deracoxib       | H46                                   |
| 299            | Deracoxib       | H47                                   |
| 300            | Deracoxib       | H48                                   |
| 301            | Deracoxib       | H49                                   |
| 302            | Deracoxib       | H50                                   |
| 303            | Deracoxib       | H51                                   |
| 304            | Deracoxib       | H52                                   |
| 305            | Deracoxib       | H53                                   |
| 306            | Deracoxib       | H54                                   |
| 307            | Deracoxib       | H55                                   |
| 308            | Deracoxib       | H56                                   |
| 309            | Deracoxib       | H57                                   |
| 310            | Deracoxib       | H58                                   |
| 311            | Deracoxib       | H59                                   |
| 312            | Deracoxib       | H60                                   |
| 313            | Deracoxib       | H61                                   |
| 314            | Deracoxib       | H62                                   |
| 315            | Deracoxib       | H63                                   |
| 316            | Deracoxib       | H64                                   |
| 317            | Deracoxib       | H65                                   |
| 318            | Deracoxib       | H66                                   |
| 319            | Deracoxib       | H67                                   |
| 320            | Deracoxib       | H68                                   |
| 321            | Deracoxib       | H69                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 322            | Deracoxib       | H70                                   |
| 323            | Deracoxib       | H71                                   |
| 324            | Deracoxib       | H72                                   |
| 325            | Deracoxib       | H73                                   |
| 326            | Deracoxib       | H74                                   |
| 327            | Deracoxib       | H75                                   |
| 328            | Deracoxib       | H76                                   |
| 329            | Deracoxib       | H77                                   |
| 330            | Deracoxib       | H78                                   |
| 331            | Deracoxib       | H79                                   |
| 332            | Deracoxib       | H80                                   |
| 333            | Deracoxib       | H81                                   |
| 334            | Deracoxib       | H82                                   |
| 335            | Deracoxib       | H83                                   |
| 336            | Deracoxib       | H84                                   |
| 337            | Etorixocib      | H1                                    |
| 338            | Etorixocib      | H2                                    |
| 339            | Etorixocib      | H3                                    |
| 340            | Etorixocib      | H4                                    |
| 341            | Etorixocib      | H5                                    |
| 342            | Etorixocib      | H6                                    |
| 343            | Etorixocib      | H7                                    |
| 344            | Etorixocib      | H8                                    |
| 345            | Etorixocib      | H9                                    |
| 346            | Etorixocib      | H10                                   |
| 347            | Etorixocib      | H11                                   |
| 348            | Etorixocib      | H12                                   |
| 349            | Etorixocib      | H13                                   |
| 350            | Etorixocib      | H14                                   |
| 351            | Etorixocib      | H15                                   |
| 352            | Etorixocib      | H16                                   |
| 353            | Etorixocib      | H17                                   |
| 354            | Etorixocib      | H18                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 355            | Etorixocib      | H19                                   |
| 356            | Etorixocib      | H20                                   |
| 357            | Etorixocib      | H21                                   |
| 358            | Etorixocib      | H22                                   |
| 359            | Etorixocib      | H23                                   |
| 360            | Etorixocib      | H24                                   |
| 361            | Etorixocib      | H25                                   |
| 362            | Etorixocib      | H26                                   |
| 363            | Etorixocib      | H27                                   |
| 364            | Etorixocib      | H28                                   |
| 365            | Etorixocib      | H29                                   |
| 366            | Etorixocib      | H30                                   |
| 367            | Etorixocib      | H31                                   |
| 368            | Etorixocib      | H32                                   |
| 369            | Etorixocib      | H33                                   |
| 370            | Etorixocib      | H34                                   |
| 371            | Etorixocib      | H35                                   |
| 372            | Etorixocib      | H36                                   |
| 373            | Etorixocib      | H37                                   |
| 374            | Etorixocib      | H38                                   |
| 375            | Etorixocib      | H39                                   |
| 376            | Etorixocib      | H40                                   |
| 377            | Etorixocib      | H41                                   |
| 378            | Etorixocib      | H42                                   |
| 379            | Etorixocib      | H43                                   |
| 380            | Etorixocib      | H44                                   |
| 381            | Etorixocib      | H45                                   |
| 382            | Etorixocib      | H46                                   |
| 383            | Etorixocib      | H47                                   |
| 384            | Etorixocib      | H48                                   |
| 385            | Etorixocib      | H49                                   |
| 386            | Etorixocib      | H50                                   |
| 387            | Etorixocib      | H51                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 388            | Etorixocib      | H52                                   |
| 389            | Etorixocib      | H53                                   |
| 390            | Etorixocib      | H54                                   |
| 391            | Etorixocib      | H55                                   |
| 392            | Etorixocib      | H56                                   |
| 393            | Etorixocib      | H57                                   |
| 394            | Etorixocib      | H58                                   |
| 395            | Etorixocib      | H59                                   |
| 396            | Etorixocib      | H60                                   |
| 397            | Etorixocib      | H61                                   |
| 398            | Etorixocib      | H62                                   |
| 399            | Etorixocib      | H63                                   |
| 400            | Etorixocib      | H64                                   |
| 401            | Etorixocib      | H65                                   |
| 402            | Etorixocib      | H66                                   |
| 403            | Etorixocib      | H67                                   |
| 404            | Etorixocib      | H68                                   |
| 405            | Etorixocib      | H69                                   |
| 406            | Etorixocib      | H70                                   |
| 407            | Etorixocib      | H71                                   |
| 408            | Etorixocib      | H72                                   |
| 409            | Etorixocib      | H73                                   |
| 410            | Etorixocib      | H74                                   |
| 411            | Etorixocib      | H75                                   |
| 412            | Etorixocib      | H76                                   |
| 413            | Etorixocib      | H77                                   |
| 414            | Etorixocib      | H78                                   |
| 415            | Etorixocib      | H79                                   |
| 416            | Etorixocib      | H80                                   |
| 417            | Etorixocib      | H81                                   |
| 418            | Etorixocib      | H82                                   |
| 419            | Etorixocib      | H83                                   |
| 420            | Etorixocib      | H84                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 421            | Lumiracoxib     | H1                                    |
| 422            | Lumiracoxib     | H2                                    |
| 423            | Lumiracoxib     | H3                                    |
| 424            | Lumiracoxib     | H4                                    |
| 425            | Lumiracoxib     | H5                                    |
| 426            | Lumiracoxib     | H6                                    |
| 427            | Lumiracoxib     | H7                                    |
| 428            | Lumiracoxib     | H8                                    |
| 429            | Lumiracoxib     | H9                                    |
| 430            | Lumiracoxib     | H10                                   |
| 431            | Lumiracoxib     | H11                                   |
| 432            | Lumiracoxib     | H12                                   |
| 433            | Lumiracoxib     | H13                                   |
| 434            | Lumiracoxib     | H14                                   |
| 435            | Lumiracoxib     | H15                                   |
| 436            | Lumiracoxib     | H16                                   |
| 437            | Lumiracoxib     | H17                                   |
| 438            | Lumiracoxib     | H18                                   |
| 439            | Lumiracoxib     | H19                                   |
| 440            | Lumiracoxib     | H20                                   |
| 441            | Lumiracoxib     | H21                                   |
| 442            | Lumiracoxib     | H22                                   |
| 443            | Lumiracoxib     | H23                                   |
| 444            | Lumiracoxib     | H24                                   |
| 445            | Lumiracoxib     | H25                                   |
| 446            | Lumiracoxib     | H26                                   |
| 447            | Lumiracoxib     | H27                                   |
| 448            | Lumiracoxib     | H28                                   |
| 449            | Lumiracoxib     | H29                                   |
| 450            | Lumiracoxib     | H30                                   |
| 451            | Lumiracoxib     | H31                                   |
| 452            | Lumiracoxib     | H32                                   |
| 453            | Lumiracoxib     | H33                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 454            | Lumiracoxib     | H34                                   |
| 455            | Lumiracoxib     | H35                                   |
| 456            | Lumiracoxib     | H36                                   |
| 457            | Lumiracoxib     | H37                                   |
| 458            | Lumiracoxib     | H38                                   |
| 459            | Lumiracoxib     | H39                                   |
| 460            | Lumiracoxib     | H40                                   |
| 461            | Lumiracoxib     | H41                                   |
| 462            | Lumiracoxib     | H42                                   |
| 463            | Lumiracoxib     | H43                                   |
| 464            | Lumiracoxib     | H44                                   |
| 465            | Lumiracoxib     | H45                                   |
| 466            | Lumiracoxib     | H46                                   |
| 467            | Lumiracoxib     | H47                                   |
| 468            | Lumiracoxib     | H48                                   |
| 469            | Lumiracoxib     | H49                                   |
| 470            | Lumiracoxib     | H50                                   |
| 471            | Lumiracoxib     | H51                                   |
| 472            | Lumiracoxib     | H52                                   |
| 473            | Lumiracoxib     | H53                                   |
| 474            | Lumiracoxib     | H54                                   |
| 475            | Lumiracoxib     | H55                                   |
| 476            | Lumiracoxib     | H56                                   |
| 477            | Lumiracoxib     | H57                                   |
| 478            | Lumiracoxib     | H58                                   |
| 479            | Lumiracoxib     | H59                                   |
| 480            | Lumiracoxib     | H60                                   |
| 481            | Lumiracoxib     | H61                                   |
| 482            | Lumiracoxib     | H62                                   |
| 483            | Lumiracoxib     | H63                                   |
| 484            | Lumiracoxib     | H64                                   |
| 485            | Lumiracoxib     | H65                                   |
| 486            | Lumiracoxib     | H66                                   |



| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 487            | Lumiracoxib     | H67                                   |
| 488            | Lumiracoxib     | H68                                   |
| 489            | Lumiracoxib     | H69                                   |
| 490            | Lumiracoxib     | H70                                   |
| 491            | Lumiracoxib     | H71                                   |
| 492            | Lumiracoxib     | H72                                   |
| 493            | Lumiracoxib     | H73                                   |
| 494            | Lumiracoxib     | H74                                   |
| 495            | Lumiracoxib     | H75                                   |
| 496            | Lumiracoxib     | H76                                   |
| 497            | Lumiracoxib     | H77                                   |
| 498            | Lumiracoxib     | H78                                   |
| 499            | Lumiracoxib     | H79                                   |
| 500            | Lumiracoxib     | H80                                   |
| 501            | Lumiracoxib     | H81                                   |
| 502            | Lumiracoxib     | H82                                   |
| 503            | Lumiracoxib     | H83                                   |
| 504            | Lumiracoxib     | H84                                   |
| 505            | Deracoxib       | H1                                    |
| 506            | Deracoxib       | H2                                    |
| 507            | Deracoxib       | H3                                    |
| 508            | Deracoxib       | H4                                    |
| 509            | Deracoxib       | H5                                    |
| 510            | Deracoxib       | H6                                    |
| 511            | Deracoxib       | H7                                    |
| 512            | Deracoxib       | H8                                    |
| 513            | Deracoxib       | H9                                    |
| 514            | Deracoxib       | H10                                   |
| 515            | Deracoxib       | H11                                   |
| 516            | Deracoxib       | H12                                   |
| 517            | Deracoxib       | H13                                   |
| 518            | Deracoxib       | H14                                   |
| 519            | Deracoxib       | H15                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 520            | Deracoxib       | H16                                   |
| 521            | Deracoxib       | H17                                   |
| 522            | Deracoxib       | H18                                   |
| 523            | Deracoxib       | H19                                   |
| 524            | Deracoxib       | H20                                   |
| 525            | Deracoxib       | H21                                   |
| 526            | Deracoxib       | H22                                   |
| 527            | Deracoxib       | H23                                   |
| 528            | Deracoxib       | H24                                   |
| 529            | Deracoxib       | H25                                   |
| 530            | Deracoxib       | H26                                   |
| 531            | Deracoxib       | H27                                   |
| 532            | Deracoxib       | H28                                   |
| 533            | Deracoxib       | H29                                   |
| 534            | Deracoxib       | H30                                   |
| 535            | Deracoxib       | H31                                   |
| 536            | Deracoxib       | H32                                   |
| 537            | Deracoxib       | H33                                   |
| 538            | Deracoxib       | H34                                   |
| 539            | Deracoxib       | H35                                   |
| 540            | Deracoxib       | H36                                   |
| 541            | Deracoxib       | H37                                   |
| 542            | Deracoxib       | H38                                   |
| 543            | Deracoxib       | H39                                   |
| 544            | Deracoxib       | H40                                   |
| 545            | Deracoxib       | H41                                   |
| 546            | Deracoxib       | H42                                   |
| 547            | Deracoxib       | H43                                   |
| 548            | Deracoxib       | H44                                   |
| 549            | Deracoxib       | H45                                   |
| 550            | Deracoxib       | H46                                   |
| 551            | Deracoxib       | H47                                   |
| 552            | Deracoxib       | H48                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 553            | Deracoxib       | H49                                   |
| 554            | Deracoxib       | H50                                   |
| 555            | Deracoxib       | H51                                   |
| 556            | Deracoxib       | H52                                   |
| 557            | Deracoxib       | H53                                   |
| 558            | Deracoxib       | H54                                   |
| 559            | Deracoxib       | H55                                   |
| 560            | Deracoxib       | H56                                   |
| 561            | Deracoxib       | H57                                   |
| 562            | Deracoxib       | H58                                   |
| 563            | Deracoxib       | H59                                   |
| 564            | Deracoxib       | H60                                   |
| 565            | Deracoxib       | H61                                   |
| 566            | Deracoxib       | H62                                   |
| 567            | Deracoxib       | H63                                   |
| 568            | Deracoxib       | H64                                   |
| 569            | Deracoxib       | H65                                   |
| 570            | Deracoxib       | H66                                   |
| 571            | Deracoxib       | H67                                   |
| 572            | Deracoxib       | H68                                   |
| 573            | Deracoxib       | H69                                   |
| 574            | Deracoxib       | H70                                   |
| 575            | Deracoxib       | H71                                   |
| 576            | Deracoxib       | H72                                   |
| 577            | Deracoxib       | H73                                   |
| 578            | Deracoxib       | H74                                   |
| 579            | Deracoxib       | H75                                   |
| 580            | Deracoxib       | H76                                   |
| 581            | Deracoxib       | H77                                   |
| 582            | Deracoxib       | H78                                   |
| 583            | Deracoxib       | H79                                   |
| 584            | Deracoxib       | H80                                   |
| 585            | Deracoxib       | H81                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 586            | Deracoxib       | H82                                   |
| 587            | Deracoxib       | H83                                   |
| 588            | Deracoxib       | H84                                   |
| 589            | Rofecoxib       | H1                                    |
| 590            | Rofecoxib       | H2                                    |
| 591            | Rofecoxib       | H3                                    |
| 592            | Rofecoxib       | H4                                    |
| 593            | Rofecoxib       | H5                                    |
| 594            | Rofecoxib       | H6                                    |
| 595            | Rofecoxib       | H7                                    |
| 596            | Rofecoxib       | H8                                    |
| 597            | Rofecoxib       | H9                                    |
| 598            | Rofecoxib       | H10                                   |
| 599            | Rofecoxib       | H11                                   |
| 600            | Rofecoxib       | H12                                   |
| 601            | Rofecoxib       | H13                                   |
| 602            | Rofecoxib       | H14                                   |
| 603            | Rofecoxib       | H15                                   |
| 604            | Rofecoxib       | H16                                   |
| 605            | Rofecoxib       | H17                                   |
| 606            | Rofecoxib       | H18                                   |
| 607            | Rofecoxib       | H19                                   |
| 608            | Rofecoxib       | H20                                   |
| 609            | Rofecoxib       | H21                                   |
| 610            | Rofecoxib       | H22                                   |
| 611            | Rofecoxib       | H23                                   |
| 612            | Rofecoxib       | H24                                   |
| 613            | Rofecoxib       | H25                                   |
| 614            | Rofecoxib       | H26                                   |
| 615            | Rofecoxib       | H27                                   |
| 616            | Rofecoxib       | H28                                   |
| 617            | Rofecoxib       | H29                                   |
| 618            | Rofecoxib       | H30                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 619            | Rofecoxib       | H31                                   |
| 620            | Rofecoxib       | H32                                   |
| 621            | Rofecoxib       | H33                                   |
| 622            | Rofecoxib       | H34                                   |
| 623            | Rofecoxib       | H35                                   |
| 624            | Rofecoxib       | H36                                   |
| 625            | Rofecoxib       | H37                                   |
| 626            | Rofecoxib       | H38                                   |
| 627            | Rofecoxib       | H39                                   |
| 628            | Rofecoxib       | H40                                   |
| 629            | Rofecoxib       | H41                                   |
| 630            | Rofecoxib       | H42                                   |
| 631            | Rofecoxib       | H43                                   |
| 632            | Rofecoxib       | H44                                   |
| 633            | Rofecoxib       | H45                                   |
| 634            | Rofecoxib       | H46                                   |
| 635            | Rofecoxib       | H47                                   |
| 636            | Rofecoxib       | H48                                   |
| 637            | Rofecoxib       | H49                                   |
| 638            | Rofecoxib       | H50                                   |
| 639            | Rofecoxib       | H51                                   |
| 640            | Rofecoxib       | H52                                   |
| 641            | Rofecoxib       | H53                                   |
| 642            | Rofecoxib       | H54                                   |
| 643            | Rofecoxib       | H55                                   |
| 644            | Rofecoxib       | H56                                   |
| 645            | Rofecoxib       | H57                                   |
| 646            | Rofecoxib       | H58                                   |
| 647            | Rofecoxib       | H59                                   |
| 648            | Rofecoxib       | H60                                   |
| 649            | Rofecoxib       | H61                                   |
| 650            | Rofecoxib       | H62                                   |
| 651            | Rofecoxib       | H63                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 652            | Rofecoxib       | H64                                   |
| 653            | Rofecoxib       | H65                                   |
| 654            | Rofecoxib       | H66                                   |
| 655            | Rofecoxib       | H67                                   |
| 656            | Rofecoxib       | H68                                   |
| 657            | Rofecoxib       | H69                                   |
| 658            | Rofecoxib       | H70                                   |
| 659            | Rofecoxib       | H71                                   |
| 660            | Rofecoxib       | H72                                   |
| 661            | Rofecoxib       | H73                                   |
| 662            | Rofecoxib       | H74                                   |
| 663            | Rofecoxib       | H75                                   |
| 664            | Rofecoxib       | H76                                   |
| 665            | Rofecoxib       | H77                                   |
| 666            | Rofecoxib       | H78                                   |
| 667            | Rofecoxib       | H79                                   |
| 668            | Rofecoxib       | H80                                   |
| 669            | Rofecoxib       | H81                                   |
| 670            | Rofecoxib       | H82                                   |
| 671            | Rofecoxib       | H83                                   |
| 672            | Rofecoxib       | H84                                   |
| 673            | Meloxicam       | H1                                    |
| 674            | Meloxicam       | H2                                    |
| 675            | Meloxicam       | H3                                    |
| 676            | Meloxicam       | H4                                    |
| 677            | Meloxicam       | H5                                    |
| 678            | Meloxicam       | H6                                    |
| 679            | Meloxicam       | H7                                    |
| 680            | Meloxicam       | H8                                    |
| 681            | Meloxicam       | H9                                    |
| 682            | Meloxicam       | H10                                   |
| 683            | Meloxicam       | H11                                   |
| 684            | Meloxicam       | H12                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 685            | Meloxicam       | H13                                   |
| 686            | Meloxicam       | H14                                   |
| 687            | Meloxicam       | H15                                   |
| 688            | Meloxicam       | H16                                   |
| 689            | Meloxicam       | H17                                   |
| 690            | Meloxicam       | H18                                   |
| 691            | Meloxicam       | H19                                   |
| 692            | Meloxicam       | H20                                   |
| 693            | Meloxicam       | H21                                   |
| 694            | Meloxicam       | H22                                   |
| 695            | Meloxicam       | H23                                   |
| 696            | Meloxicam       | H24                                   |
| 697            | Meloxicam       | H25                                   |
| 698            | Meloxicam       | H26                                   |
| 699            | Meloxicam       | H27                                   |
| 700            | Meloxicam       | H28                                   |
| 701            | Meloxicam       | H29                                   |
| 702            | Meloxicam       | H30                                   |
| 703            | Meloxicam       | H31                                   |
| 704            | Meloxicam       | H32                                   |
| 705            | Meloxicam       | H33                                   |
| 706            | Meloxicam       | H34                                   |
| 707            | Meloxicam       | H35                                   |
| 708            | Meloxicam       | H36                                   |
| 709            | Meloxicam       | H37                                   |
| 710            | Meloxicam       | H38                                   |
| 711            | Meloxicam       | H39                                   |
| 712            | Meloxicam       | H40                                   |
| 713            | Meloxicam       | H41                                   |
| 714            | Meloxicam       | H42                                   |
| 715            | Meloxicam       | H43                                   |
| 716            | Meloxicam       | H44                                   |
| 717            | Meloxicam       | H45                                   |

| Example Number | Cox-2 Inhibitor | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-----------------|---------------------------------------|
| 718            | Meloxicam       | H46                                   |
| 719            | Meloxicam       | H47                                   |
| 720            | Meloxicam       | H48                                   |
| 721            | Meloxicam       | H49                                   |
| 722            | Meloxicam       | H50                                   |
| 723            | Meloxicam       | H51                                   |
| 724            | Meloxicam       | H52                                   |
| 725            | Meloxicam       | H53                                   |
| 726            | Meloxicam       | H54                                   |
| 727            | Meloxicam       | H55                                   |
| 728            | Meloxicam       | H56                                   |
| 729            | Meloxicam       | H57                                   |
| 730            | Meloxicam       | H58                                   |
| 731            | Meloxicam       | H59                                   |
| 732            | Meloxicam       | H60                                   |
| 733            | Meloxicam       | H61                                   |
| 734            | Meloxicam       | H62                                   |
| 735            | Meloxicam       | H63                                   |
| 736            | Meloxicam       | H64                                   |
| 737            | Meloxicam       | H65                                   |
| 738            | Meloxicam       | H66                                   |
| 739            | Meloxicam       | H67                                   |
| 740            | Meloxicam       | H68                                   |
| 741            | Meloxicam       | H69                                   |
| 742            | Meloxicam       | H70                                   |
| 743            | Meloxicam       | H71                                   |
| 744            | Meloxicam       | H72                                   |
| 745            | Meloxicam       | H73                                   |
| 746            | Meloxicam       | H74                                   |
| 747            | Meloxicam       | H75                                   |
| 748            | Meloxicam       | H76                                   |
| 749            | Meloxicam       | H77                                   |
| 750            | Meloxicam       | H78                                   |



| Example Number | Cox-2 Inhibitor               | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-------------------------------|---------------------------------------|
| 751            | Meloxicam                     | H79                                   |
| 752            | Meloxicam                     | H80                                   |
| 753            | Meloxicam                     | H81                                   |
| 754            | Meloxicam                     | H82                                   |
| 755            | Meloxicam                     | H83                                   |
| 756            | Meloxicam                     | H84                                   |
| 757            | A chromene<br>Cox-2 inhibitor | H1                                    |
| 758            | A chromene<br>Cox-2 inhibitor | H2                                    |
| 759            | A chromene<br>Cox-2 inhibitor | H3                                    |
| 760            | A chromene<br>Cox-2 inhibitor | H4                                    |
| 761            | A chromene<br>Cox-2 inhibitor | H5                                    |
| 762            | A chromene<br>Cox-2 inhibitor | H6                                    |
| 763            | A chromene<br>Cox-2 inhibitor | H7                                    |
| 764            | A chromene<br>Cox-2 inhibitor | H8                                    |
| 765            | A chromene<br>Cox-2 inhibitor | H9                                    |
| 766            | A chromene<br>Cox-2 inhibitor | H10                                   |
| 767            | A chromene<br>Cox-2 inhibitor | H11                                   |
| 768            | A chromene<br>Cox-2 inhibitor | H12                                   |
| 769            | A chromene<br>Cox-2 inhibitor | H13                                   |
| 770            | A chromene<br>Cox-2 inhibitor | H14                                   |
| 771            | A chromene<br>Cox-2 inhibitor | H15                                   |
| 772            | A chromene<br>Cox-2 inhibitor | H16                                   |
| 773            | A chromene<br>Cox-2 inhibitor | H17                                   |
| 774            | A chromene<br>Cox-2 inhibitor | H18                                   |

| Example Number | Cox-2 Inhibitor               | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-------------------------------|---------------------------------------|
| 775            | A chromene<br>Cox-2 inhibitor | H19                                   |
| 776            | A chromene<br>Cox-2 inhibitor | H20                                   |
| 777            | A chromene<br>Cox-2 inhibitor | H21                                   |
| 778            | A chromene<br>Cox-2 inhibitor | H22                                   |
| 779            | A chromene<br>Cox-2 inhibitor | H23                                   |
| 780            | A chromene<br>Cox-2 inhibitor | H24                                   |
| 781            | A chromene<br>Cox-2 inhibitor | H25                                   |
| 782            | A chromene<br>Cox-2 inhibitor | H26                                   |
| 783            | A chromene<br>Cox-2 inhibitor | H27                                   |
| 784            | A chromene<br>Cox-2 inhibitor | H28                                   |
| 785            | A chromene<br>Cox-2 inhibitor | H29                                   |
| 786            | A chromene<br>Cox-2 inhibitor | H30                                   |
| 787            | A chromene<br>Cox-2 inhibitor | H31                                   |
| 788            | A chromene<br>Cox-2 inhibitor | H32                                   |
| 789            | A chromene<br>Cox-2 inhibitor | H33                                   |
| 790            | A chromene<br>Cox-2 inhibitor | H34                                   |
| 791            | A chromene<br>Cox-2 inhibitor | H35                                   |
| 792            | A chromene<br>Cox-2 inhibitor | H36                                   |
| 793            | A chromene<br>Cox-2 inhibitor | H37                                   |
| 794            | A chromene<br>Cox-2 inhibitor | H38                                   |
| 795            | A chromene<br>Cox-2 inhibitor | H39                                   |
| 796            | A chromene<br>Cox-2 inhibitor | H40                                   |

| Example Number | Cox-2 Inhibitor               | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-------------------------------|---------------------------------------|
| 797            | A chromene<br>Cox-2 inhibitor | H41                                   |
| 798            | A chromene<br>Cox-2 inhibitor | H42                                   |
| 799            | A chromene<br>Cox-2 inhibitor | H43                                   |
| 800            | A chromene<br>Cox-2 inhibitor | H44                                   |
| 801            | A chromene<br>Cox-2 inhibitor | H45                                   |
| 802            | A chromene<br>Cox-2 inhibitor | H46                                   |
| 803            | A chromene<br>Cox-2 inhibitor | H47                                   |
| 804            | A chromene<br>Cox-2 inhibitor | H48                                   |
| 805            | A chromene<br>Cox-2 inhibitor | H49                                   |
| 806            | A chromene<br>Cox-2 inhibitor | H50                                   |
| 807            | A chromene<br>Cox-2 inhibitor | H51                                   |
| 808            | A chromene<br>Cox-2 inhibitor | H52                                   |
| 809            | A chromene<br>Cox-2 inhibitor | H53                                   |
| 810            | A chromene<br>Cox-2 inhibitor | H54                                   |
| 811            | A chromene<br>Cox-2 inhibitor | H55                                   |
| 812            | A chromene<br>Cox-2 inhibitor | H56                                   |
| 813            | A chromene<br>Cox-2 inhibitor | H57                                   |
| 814            | A chromene<br>Cox-2 inhibitor | H58                                   |
| 815            | A chromene<br>Cox-2 inhibitor | H59                                   |
| 816            | A chromene<br>Cox-2 inhibitor | H60                                   |
| 817            | A chromene<br>Cox-2 inhibitor | H61                                   |
| 818            | A chromene<br>Cox-2 inhibitor | H62                                   |

| Example Number | Cox-2 Inhibitor               | 5-HT <sub>1A</sub> Receptor Modulator |
|----------------|-------------------------------|---------------------------------------|
| 819            | A chromene<br>Cox-2 inhibitor | H63                                   |
| 820            | A chromene<br>Cox-2 inhibitor | H64                                   |
| 821            | A chromene<br>Cox-2 inhibitor | H65                                   |
| 822            | A chromene<br>Cox-2 inhibitor | H66                                   |
| 823            | A chromene<br>Cox-2 inhibitor | H67                                   |
| 824            | A chromene<br>Cox-2 inhibitor | H68                                   |
| 825            | A chromene<br>Cox-2 inhibitor | H69                                   |
| 826            | A chromene<br>Cox-2 inhibitor | H70                                   |
| 827            | A chromene<br>Cox-2 inhibitor | H71                                   |
| 828            | A chromene<br>Cox-2 inhibitor | H72                                   |
| 829            | A chromene<br>Cox-2 inhibitor | H73                                   |
| 830            | A chromene<br>Cox-2 inhibitor | H74                                   |
| 831            | A chromene<br>Cox-2 inhibitor | H75                                   |
| 832            | A chromene<br>Cox-2 inhibitor | H76                                   |
| 833            | A chromene<br>Cox-2 inhibitor | H77                                   |
| 834            | A chromene<br>Cox-2 inhibitor | H78                                   |
| 835            | A chromene<br>Cox-2 inhibitor | H79                                   |
| 836            | A chromene<br>Cox-2 inhibitor | H80                                   |
| 837            | A chromene<br>Cox-2 inhibitor | H81                                   |
| 838            | A chromene<br>Cox-2 inhibitor | H82                                   |
| 839            | A chromene<br>Cox-2 inhibitor | H83                                   |
| 840            | A chromene<br>Cox-2 inhibitor | H84                                   |

### Biological Assays

#### Evaluation of Cox-1 and Cox-2 activity *in vitro*:

5     **[000246]** The Cox-2 inhibiting agents of this invention exhibit Cox-2 inhibition *in vitro*. The Cox-2 inhibition activity of the compounds illustrated in the example above are determined by the following methods. The Cox-2 inhibition activity of the other Cox-2 inhibitors of the present invention may also be determined by the following methods.

#### Preparation of recombinant Cox baculoviruses:

10    **[000247]** Recombinant Cox-1 and Cox-2 are prepared as described by Gierse et al., [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine Cox-1 or human or murine Cox-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors  
15    for Cox-1 and Cox-2 in a manner similar to the method of D.R. O'Reilly et al. (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2x10<sup>8</sup>) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate  
20    method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (10<sup>7</sup>-10<sup>8</sup> pfu/mL) stocks of virus are prepared. For large scale production, SF9 insect cells are  
25    infected in 10 liter fermentors (0.5 x 10<sup>6</sup>/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is  
30    centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for Cox activity.

Assay for Cox-1 and Cox-2 activity:

[000248] Cox activity is assayed as PGE<sub>2</sub> formed/ $\mu$ g protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate Cox enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10  $\mu$ M).

Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C/room temperature by transferring 40  $\mu$ l of reaction mix into 160  $\mu$ l ELISA buffer and 25  $\mu$ M indomethacin. The PGE<sub>2</sub> formed is measured by standard ELISA technology (Cayman Chemical).

Fast assay for Cox-1 and Cox-2 activity:

[000249] Cox activity is assayed as PGE<sub>2</sub> formed/ $\mu$ g protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate Cox enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2  $\mu$ M phenol, 1  $\mu$ M heme, 300  $\mu$ M epinephrine) with the addition of 20  $\mu$ l of 100  $\mu$ M arachidonic acid (10  $\mu$ M). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic acid.

Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C/room temperature by transferring 40  $\mu$ l of reaction mix into 160  $\mu$ l ELISA buffer and 25  $\mu$ M indomethacin. The PGE<sub>2</sub> formed is measured by standard ELISA technology (Cayman Chemical).

Evaluation of 5-HT<sub>1A</sub> Activity *in vitro*5-HT<sub>1A</sub> Receptor Binding Profile:

[000250] Compounds are tested for binding to cloned human 5-HT<sub>1A</sub> receptors stably transfected into CHO cells using [<sup>3</sup>H]8-OH-DPAT as the

5-HT<sub>1A</sub> radioligand (according to general procedure described in J. Dunlop *et al.*, *J. Pharmacol. Tox. Methods*, 40:47-55 (1998)).

5-HT<sub>1A</sub> Functional Activity Assay:

5 [000251] A clonal cell line stably transfected with the human 5-HT<sub>1A</sub> receptor is utilized to determine the intrinsic activity of compounds (according to the general procedure described in J. Dunlop *et al.*, *J. Pharmacol. Tox. Methods*, 40:47-55 (1998)). Compounds of the present invention are tested for their efficacy in antagonizing the ability of 10 nM 8-OH-DPAT to inhibit forskolin stimulated cAMP production in a  
10 concentration-related fashion.

Biological Evaluation:

[000252] A combination therapy of a Cox-2 inhibiting agent and a 5-HT<sub>1A</sub> receptor modulator for the treatment or prevention of pain, inflammation, or an inflammation-related disorder in a mammal can be evaluated as  
15 described in the following tests.

Rat focal stroke model:

[000253] The efficacy of the compositions of the present invention for the prevention and treatment of focal stroke in rats can be determined according to the method described in Nogawa, S. *et al.*, *J. of Neuroscience*, 17(8):2748-2755 (1997).  
20

Induction and Assessment of Collagen Induced Arthritis in Mice:

[000254] Arthritis is induced in 8-12 week old male DBA/1 mice by injection of 50 mg of chick type II collagen (CII) in complete Freund's adjuvant (Sigma) on day 0 at the base of the tail as previously described [J. Stuart, *Annual Rev. Immunol.*, 2:199 (1984)]. Compounds are prepared  
25 as a suspension in 0.5% methylcellulose (Sigma, St. Louis, MO), 0.025% Tween 20 (Sigma). The Cox-2 inhibitors and the 5-HT<sub>1A</sub> receptor modulator are administered alone or a Cox-2 inhibitor and 5-HT<sub>1A</sub> receptor modulator in combination. The compounds are administered in non-

arthritic animals by gavage in a volume of 0.1 ml beginning on day 20 post collagen injection and continuing daily until final evaluation on day 55.

**[000255]** Animals are boosted on day 21 with 50 mg of collagen (CII) in incomplete Freund's adjuvant. The animals are subsequently evaluated several times each week for incidence and severity of arthritis until approximately day 56. Any animal with paw redness or swelling is counted as arthritic. Scoring of severity is carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as previously described [P.

Wooley, *et al.*, *Trans. Proc.*, 15:180 (1983)]. The animals are measured for incidence of arthritis and severity in the animals where arthritis is observed. The incidence of arthritis is determined at a gross level by observing the swelling or redness in the paw or digits. Severity is measured with the following guidelines. Briefly, animals displaying four normal paws, *i.e.*, no redness or swelling are scored 0. Any redness or swelling of digits or the paw is scored as 1. Gross swelling of the whole paw or deformity is scored as 2. Ankylosis of joints is scored as 3.

Histological Examination of Paws:

**[000256]** In order to verify the gross determination of a non-arthritic animal, a histological examination is performed. Paws from animals sacrificed at the end of the experiment are removed, fixed and decalcified as previously described [R. Jonsson, *J. Immunol. Methods*, 88:109 (1986)]. Samples are paraffin embedded, sectioned, and stained with hematoxylin and eosin by standard methods. Stained sections are examined for cellular infiltrates, synovial hyperplasia, and bone and cartilage erosion.

**[000257]** All references cited in this specification, including without limitation all papers, publications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any



reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000258] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

5 [000259] While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular  
10 dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the methods, combinations and compositions of the present invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to  
15 and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended,  
20 therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

**WHAT IS CLAIMED IS:**

1. A composition comprising a Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator.
2. The composition according to claim 1, wherein the amount of  
5 the Cox-2 inhibitor and the amount of the 5-HT<sub>1A</sub> receptor modulator  
together comprise a therapeutically effective amount for the treatment or  
prevention of pain, inflammation or an inflammation-related disorder.
3. The composition according to claim 1, wherein the Cox-2  
inhibitor comprises a non-steroidal anti-inflammatory drug.
- 10 4. The composition according to claim 3, wherein the Cox-2  
inhibitor is selected from the group consisting of ibuprofen, naproxen,  
benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen,  
pirprofen, carprofen, oxaprozin, prapoprofen, miroprofen, tioxaprofen,  
suprofen, alminoprofen, tiaprofenic acid, fluprofen, bucloxic acid,  
15 indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenec,  
alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acetyl  
salicylic acid, indometacin, piroxicam, tenoxicam, nabumetone, ketorolac,  
azapropazone, mefenamic acid, tolfenamic acid, diflunisal,  
podophyllotoxin derivatives, acetaminophen, dextrofen, flosafenine,  
20 oxyphenbutazone, phenylbutazone, proglumetacin, acetaminophen, fentiazac,  
clidanac, oxipinac, mefenamic acid, meclofenamic acid, flufenamic acid,  
niflumic acid, flufenisal, sudoxicam, etodolac, pirofen, salicylic acid,  
choline magnesium trisalicylate, salicylate, benorylate, fentiazac, clopinac,  
feprazone, isoxicam, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-  
25 (nitrooxy)butyl ester.
5. The composition according to claim 4, wherein the Cox-2  
inhibitor comprises 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-  
(nitrooxy)butyl ester.
6. The composition according to claim 1, wherein the Cox-2  
30 inhibitor comprises a Cox-2 selective inhibitor.

7. The composition according to claim 6, wherein the Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, deracoxib, parecoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, and mixtures and prodrugs thereof.

5 8. The composition according to claim 7, wherein the Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, valdecoxib, rofecoxib, and mixtures thereof.

9. The composition according to claim 1, wherein the Cox-2 selective inhibitor comprises a chromene Cox-2 selective inhibitor.

10 10. The composition according to claim 1, wherein the 5-HT<sub>1A</sub> receptor modulator comprises at least one compound selected from the group consisting of:

(R)-N-(1,3-benzodioxol-5-ylmethyl)-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine-3-carboxamide (AP-521), 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1H)-quinolinone (OPC-14523), 2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (DU-125530), 7-(4-methyl-1-piperazinyl)-2(3H)benzoxazolone, monohydrochloride (SLV-308), adatsanerin, alnespirone, binospirone, buspirone, DU-127090, E-2101, eptapirone, flibanserin, gepirone, ipsapirone, lesopitron, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamidetrihydrochloride (WAY-100635), N-[3-(1,3-benzodioxol-5-yloxy)propyl]-2,3-dihydro-(2S)-1,4-benzodioxin-2-methanaminehydrochloride (MKC-242), repinotan, robalzotan, sarizotan, SLV-319, SUN-N4057, tandospirone, vilazodone, VML-670, xaliproden, ziprasidone, 6-hydroxy-buspirone, pyrazolidine derivative, heteroaryloxyethylamines, 5-hydroxytryptamine, 5-methoxytryptamine, buspirone, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), ipsaspirone, gepirone, SM23997, lysergic acid diethylamide, agonistic antibodies, piperazine derivatives, 8-(2-aminoalkoxy) fluoro chroman

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derivatives, abeo-ergoline derivatives, A-74283, AP-159, AZ 16596, 2- [4-(2-methoxyphenyl)piperazin-1-yl] methyl] octahydroimidazo [1,5-a] pyridine-1,3-dione (B 20991), BMS 181100 (BMY 42569), BMS 181970, 1-methyl-4- [7-(4-chlorophenyl)methylaminocarbonyl] naphthyl-piperazine (CP291952), (omega-piperazinylalkoxy) alkylendioxybenzene (BP 554), E 5165, E 6265, ebalzotan, eltoprazine, F 11440, F 13714, flesinoxan, 2- [4-(3-phenylpyrrolidin-1-yl)butyl] -1,2-benzisothiazol-3(2H)-one 1,1-dioxide (LB 50016), LY 41, (+/-)-4-substituted-amino-6-substituted-1,3,4,5-tetrahydrobenz[c,d]inoles (LY 228729), LY 228730, LY 274600, LY 274601, LY 293284, 6-heterocyclyl-4-amino-1,3,4,5-tetrahydrobenz CD indoles (LY 297996), isoxazole derivatives (LY 315535), hetero-oxy alkanamines (LY 333068), LY 426965, LY 433221, MDL 72832, MDL 73975, NDL 249, nerisopam, Org 1301, 2-(2-oxo-hexahydropyrimidin-1-yl)propylaminomethyl- benzopyran (R 137696), RU 24969, 1-[[5-[[4-substituted-1-piperazinyl]methyl]-pyrrol-2-yl or furan-2-yl]methyl-2-piperidinones (RWJ 25730), S 14489, S 14506, S 14671, S 15535, S 15931, 8- [4- [N-(5-Acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)-Npropylamino] butyl] -8-azaspiro [4.5] decane-7,9-dione (S 23751), SDZ 216-525, SEP 109235, SR 59026, Sunepitron, UH 301, WAY 100135, WAY 100802, [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-[(5-methyl-pyridin-2-ylmethyl)amino]-methyl]piperidin-1-yl]-methadone] (F 13640), zalospirone, a pharmaceutically acceptable salt of any one of the compounds, and mixtures of two or more of the compounds.

11. The composition according to claim 1, wherein the 5-HT<sub>1A</sub> receptor modulator comprises at least one compound that is selected from the group consisting of buspirone, gepirone, repinotan, tandospirone, xaliprodol, ziprasidone, and mixtures thereof.

12. A method for the treatment or prevention of pain, inflammation, or inflammation-related disorder in a subject in need thereof,

comprising administering to the subject a Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator.

13. The method according to claim 12, wherein the amount of the Cox-2 inhibitor and the amount of the 5-HT<sub>1A</sub> receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation or an inflammation-related disorder in the subject.

14. The method according to claim 12, wherein the Cox-2 inhibitor comprises at least one non-steroidal anti-inflammatory drug that is selected from the group consisting of ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, prapoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenec, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acetyl salicylic acid, indometacin, piroxicam, tenoxicam, nabumetone, ketorolac, azapropazone, mefenamic acid, tolfenamic acid, diflunisal, podophyllotoxin derivatives, acetaminophen, dextrofen, flosal, oxyphenbutazone, phenylbutazone, proglumetacin, acetaminophen, fentiazac, clidanac, oxipinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, flufenisal, sudoxicam, etodolac, piroprofen, salicylic acid, choline magnesium trisalicylate, salicylate, benorylate, fentiazac, clopinac, feprazone, isoxicam, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

15. The method according to claim 12, wherein the Cox-2 inhibitor comprises a Cox-2 selective inhibitor.

16. The method according to claim 12, wherein the Cox-2 selective inhibitor comprises at least one compound that is selected from the group consisting of celecoxib, deracoxib, valdecoxib, parecoxib, lumiracoxib, rofecoxib, etoricoxib, meloxicam, and mixtures and prodrugs thereof.

17. The method according to claim 12, wherein the Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, parecoxib, rofecoxib, and mixtures thereof.

18. The method according to claim 12, wherein the 5-HT<sub>1A</sub> receptor modulator comprises at least one compound selected from the group consisting of:

(R)-N-(1,3-benzodioxol-5-ylmethyl)-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine-3-carboxamide (AP-521), 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1H)-quinolinone (OPC-14523), 2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (DU-125530), 7-(4-methyl-1-piperazinyl)-2(3H)benzoxazolone, monohydrochloride (SLV-308), adatsanerin, alnespirone, binospirone, buspirone, DU-127090, E-2101, eptapirone, flibanserin, gepirone, ipsapirone, lesopitron, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamidetrihydrochloride (WAY-100635), N-[3-(1,3-benzodioxol-5-yloxy)propyl]-2,3-dihydro-(2S)-1,4-benzodioxin-2-methanaminehydrochloride (MKC-242), repinotan, robalzotan, sarizotan, SLV-319, SUN-N4057, tandospirone, vilazodone, VML-670, xaliproden, ziprasidone, 6-hydroxy-buspirone, pyrazolidine derivative, heteroaryloxyethylamines, 5-hydroxytryptamine, 5-methoxytryptamine, buspirone, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), ipsaspirone, gepirone, SM23997, lysergic acid diethylamide, agonistic antibodies, piperazine derivatives, 8-(2-aminoalkoxy) fluoro chroman derivatives, abeo-ergoline derivatives, A-74283, AP-159, AZ 16596, 2-[4-(2-methoxyphenyl)piperazin-1-yl] methyl] octahydroimidazo [1,5-a] pyridine-1,3-dione (B 20991), BMS 181100 (BMV 42569), BMS 181970, 1-methyl-4-[7-(4-chlorophenyl)methylaminocarbonyl] naphthyl-piperazine (CP291952), (omega-piperazinylalkoxy) alkylenedioxybenzene (BP 554), E 5165, E 6265, ebalzotan, eltoprazine, F 11440, F 13714, flesinoxan, 2-[4-(3-phenylpyrrolidin-1-yl)butyl]

-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (LB 50016), LY 41, (+/-)-4-Substituted-amino-6-substituted-1,3,4,5-tetrahydrobenz[c,d]indoles (LY 228729), LY 228730, LY 274600, LY 274601, LY 293284, 6-heterocycl-4-amino-1,3,4,5-tetrahydrobenz CD indoles (LY 297996),  
5 isoxazole derivatives (LY 315535), hetero-oxy alkanamines, (LY 333068), LY 426965, LY 433221, MDL 72832, MDL 73975, NDL 249, nerisopam, Org 1301, 2-(2-oxo-hexahydropyrimidin-1-yl)propylaminomethyl-benzopyran (R 137696), RU 24969, 1-[[5-[[4-substituted-1-piperazinyl]methyl]-pyrrol-2-yl or furan-2-yl]methyl-2-piperidinones (RWJ  
10 25730), S 14489, S 14506, S 14671, S 15535, S 15931, 8- [4- [N-(5-Acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)-Npropylamino] butyl] -8-azaspiro [4.5] decane-7,9-dione (S 23751), SDZ 216-525, SEP 109235, SR 59026, Sunepitron, UH 301, WAY 100135, WAY 100802, [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-[[[(5-methyl-pyridin-2-ylmethyl)amino]-methyl]piperidin-1-yl]-methadone] (F 13640), zalospirone, and mixtures thereof.

or a pharmaceutically acceptable salt of the compound.

19. The method according to claim 12, wherein the 5-HT<sub>1A</sub> receptor modulator comprises at least one compound that is selected from the group consisting of of buspirone, gepirone, repinotan, tandospirone,  
20 xaliproden, ziprasidone, and mixtures thereof.

20. The method according to claim 12, wherein the inflammation-related disorder is selected from the group consisting of central nervous system disorder, cognitive dysfunction, and glaucoma.

21. The method according to claim 20, wherein the central  
25 nervous system disorder is a disorder associated with stroke (ischemic or hemorrhagic) or ischemic brain injury.

22. The method according to claim 12, wherein the pain, inflammation or inflammation related disorder is selected from the group consisting of adjustment disorders, anxiety (mixed anxiety), mood  
30 (depressed), conduct disturbance, mixed anxiety and mood (conduct), addictive disorders, alcohol abuse, intoxication disorders, nicotine abuse,

psychoactive substances abuse, substance disorder, withdrawal syndromes, acute trauma, age associated mental disorders, learning disorders, Alzheimer's disease, agitation disorders, agitation in Alzheimer's disease, agitation in the elderly, aggressive behavior, aggressive behavior in Alzheimers disease, amyloidosis, aging / senile amyloidosis, hereditary amyloidosis, immunocyte derived amyloidosis, lichen amyloidosis, primary amyloidosis, reactive systemic amyloidosis, secondary amyloidosis, senile amyloidosis (Alzheimer's disease), amyotrophy & amyotrophic lateral sclerosis (ALS), ALS, anorexia nervosa, anxiety disorders, generalized anxiety disorder (GAD), social phobias, stress related diseases, apathy, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), autism, auto immune disorders, lupus erythematosus, multiple sclerosis, behavioral disturbances, agitation plus diminished cognition, bipolar I disorder, bipolar II disorder, bulimia nervosa, cardiovascular disorders, blood pressure modification, hypertension, hypotension, heart rate modification, chemotherapy-induced vomiting, chronic fatigue immune disorders (CFIDS), chronic fatigue syndrome (CFS), cognitive dysfunction, cortical dementias, mild cognitive impairment (MCI), Lewy Body dementia, vascular dementia, neurodegeneration, cognitive dysfunction resulting from stroke, ischemia, trauma, or surgical procedures, including coronary artery bypass surgery, cognition enhancement, conduct disorder, cyclothymia, delusional disorder, depression, adolescent depression, depression in Alzheimer's disease, general depression, minor depression, depression in Parkinson's disease, depression in diabetic neuropathy, dissociative disorders, developmental disorders, learning disabilities, language disorders, mental retardation, dementia, dementias associated with aging, illness, neurodegeneration and dyskinesia, dysthymia, dystonia, eating disorders associated with anorexia nervosa, bulimia nervosa, obesity, epilepsy, or fibromyalgia syndrome (FMS), gastrointestinal disorders, irritable bowel syndrome, psychogenic effects and stress-related; growth retardation effects, endocrine, psychosocial and stress-related retardation, heart rate



modification, Huntington's chorea, hypertension, immune system disorders, immune system depression, impulse control disorders, incontinence, infectious neuropathy, AIDS, carpal tunnel syndrome, dementia, irritable bowel syndrome (IBS), constipative IBS, diarrhea-  
5 predominant IBS, inflammatory bowel disease (IBD), constipation-  
predominant IBD, diarrhea-predominant IBD, mixed states IBD, inhalation disorder, lactation inhibition, metabolic & chromosomal disorders, galactosemia phenylketonuria, fatty acid disorder, infantile nephropathic cystinosis, orthithrotranscarbamylase porphyria, migrane, mood disorders,  
10 atypical depression, bipolar disorder (including psychotic features), major depressive disorder, mania, seasonal affective disorder, movement disorders, athetosis, chorea, dyskinesia, dystonia, restless leg syndrome (RLS), tremor plus periodic limb movement (PLM), periodic limb movements of sleep (PLMS), Parkinson's disease, PLM, PLMS,  
15 progressive supranuclear palsy, stereotypy (various), torticollis, tic disorders, tremor; multisystemic atrophy (MSA), multiple sclerosis, neuroendocrine system disorders, neurodegenerative disorders, amyotrophy, amyotrophy diabetics, amyotrophic lateral sclerosis (ALS), Parkinson's disease, neurological disorders, neuropathy, diabetic  
20 neuropathy, peripheral neuropathy, neuroprotective effects for ischemic brain injury, neuroprotective effects for myocardial infarction, neuroprotective effects for spinal cord injury, neuroprotective effects for traumatic brain injury, neuroprotective effects for obesity, obsessive compulsive disorder (OCD), oncology related disorders, behavior  
25 abnormalities resulting from tumors or treatments, oppositional defiant disorder, pain disorders, acute pain, chronic pain, cluster headache, dysmenorrhea, labor pain, migraine pain, neuropathic pain, AIDs-related pain, AIDS-associated dementia, cancer-related pain, chemotherapeutic-induced pain, diabetic pain, post-herpetic neuralgia, radiation-induced  
30 pain, osteoarthritis flare, phantom limb pain, surgical pain, post-surgical pain, incisional pain, psychic pain, regional pain, abdominal pain, chronic back pain, complex-regional pain disorder, dental, face and mouth pain,

head pain, lower back and peripheral pain, rheumatoid arthritis pain, starting pain, systematic pain, connective tissue pain, musculoskeletal pain, nervous system pain, urogenital pain, uterine contraction pain, panic disorder, agoraphobia, peripheral neuropathy, personality disorders, phobias (simple), phobias of animals, phobias of closed spaces (claustrophobia), phobias of heights (acrophobia), phobias of public places (agoraphobia), social phobias, phobia of public eating, phobia of public embarrassment, phobia of public performance / speaking and using public lavatories, poop out syndrome, SSRI, post-traumatic stress disorder, progressive supranuclear palsy (PSP), prolactin plasma level disorders, psychotic disorders, brief psychosis, long duration psychosis, psychosis due to medical condition, restless leg syndrome (RLS), schizophrenias, delusional (paranoid) disorder, schizoaffective disorders, schizophreniform disorders, seasonal affective disorder, seizure disorders, epilepsy (partial), epilepsy (generalized), sexual dysfunction, sleep disorders, apnea, parasomnias, insomnia, narcolepsy, obstructive sleep disorder, disorders of circadian rhythm, enuresis, initiation, or maintenance, social phobias, social anxiety disorder, somatoform disorders, conversion, body, dysmorphic somatoform disorder, fibromyalgia syndrome (FMS), hypochondriasis, NOS, somatization, undifferentiated somatoform disorder, developmental disorders, stress disorders, acute stress disorder, chronic stress disorder, incontinence, spectrum disorders, stroke, suicidal behavior, thyroid stimulating hormone disorders (TSH), Tourette's syndrome, tooth-germ morphogenesis disorders, thermoregulation disorders, TSH modulating agent disorders, tic disorders, trauma, acute trauma, head trauma, vasospasms, vasoreactive headaches and violent behavior.

23. The method of claim 12, wherein the subject is a mammal.

24. A pharmaceutical composition for the treatment or prevention of pain, inflammation, or inflammation-related disorder, the

pharmaceutical composition comprising a Cox-2 inhibitor, a 5-HT<sub>1A</sub> receptor modulator, and a pharmaceutically-acceptable excipient.

25. A kit that is suitable for use in the treatment or prevention of pain, inflammation, or inflammation-related disorder wherein the kit  
5 comprises a first dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a 5-HT<sub>1A</sub> receptor modulator, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention or inhibition of pain, inflammation, or an inflammation-related disorder.

10 26. A method for the prevention or treatment of a neurologic disorder involving neurodegeneration in a subject that is in need of such prevention or treatment, the method comprising administering to the subject a Cox-2 inhibitor and a 5-HT<sub>1A</sub> receptor modulator.